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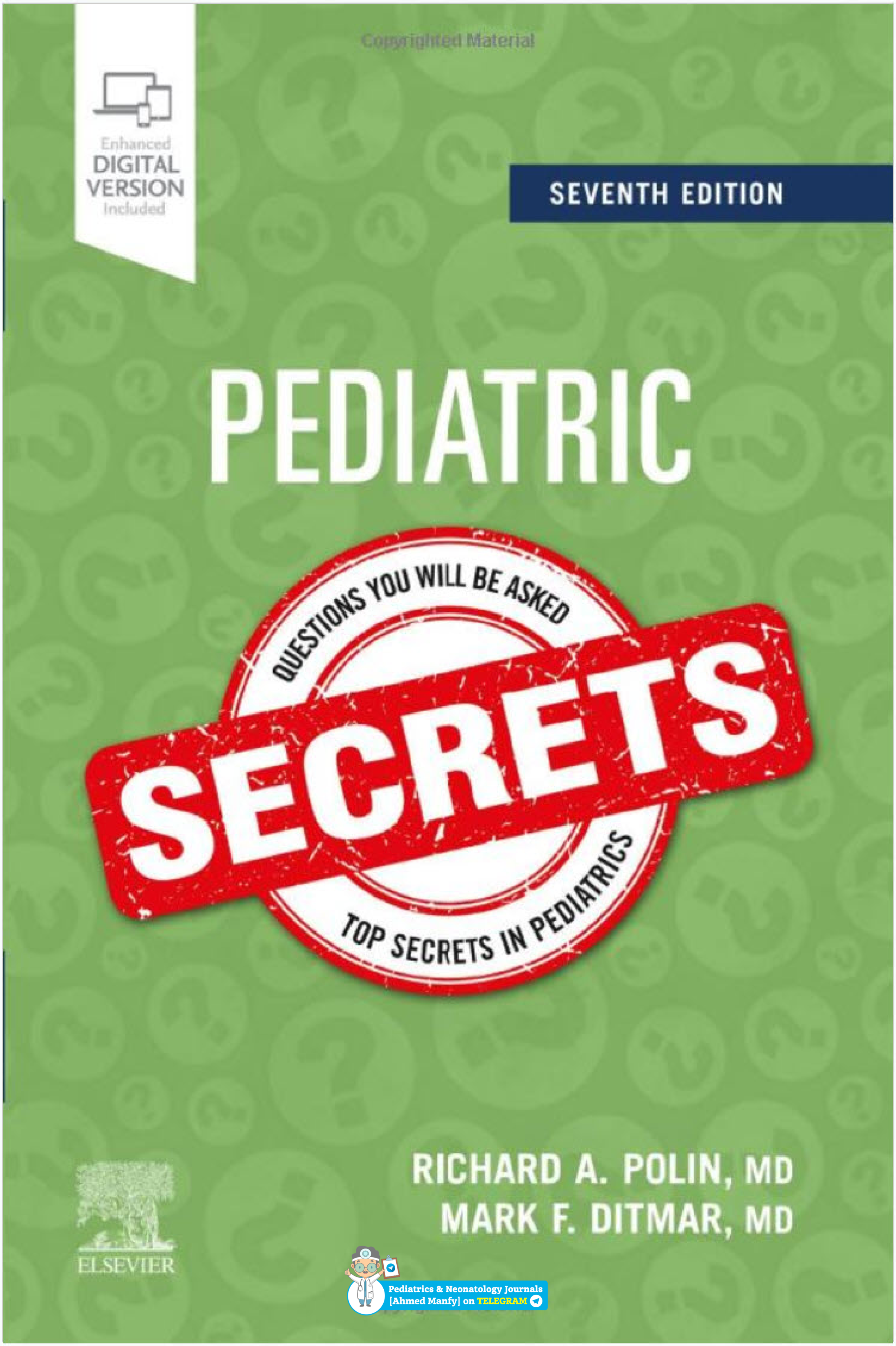

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RICHARD A. POLIN, MD
MARK F. DITMAR, MD

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PEDIATRIC SECRETS

SECRETS

SEVENTH EDITION

PEDIATRIC SECRETS

SECRETS

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OUR INSPIRATIONS

PREFACE

In the preface to the first edition of *Pediatric Secrets* more than 30 years ago, we noted that it was through constant questioning and reappraisal that patient care was improved. As the Chinese proverb observed, “One who asks a question may be a fool for five minutes, but one who does not ask a question remains a fool forever.” The intent of this series has been to pose questions that might commonly be asked in varied settings: a pediatric inpatient unit, specialty clinic, or primary care office.

With the publication of the seventh edition, we have tried to remain true to the spirit of earlier editions by incorporating both topics that examine fundamentals of pediatric care involving pathophysiologic principles, differential diagnoses, and evidence-based treatments as well as those of clinical controversy and uncertainty that might pique a reader’s interest to explore in greater detail.

As we publish this 7th edition, the world continues to reel from the seismic effects of the COVID-19 pandemic. The extent of the virus’s impact on the health of children continues to evolve. The clinical and socioeconomic consequences will be felt by all who care for pediatric patients in the coming years.

Since the sixth edition, we have lost a wonderful colleague, Dr. Ralph Schrager, who was a gifted neonatologist and an inspirational friend. He is very much missed. We dedicate the seventh edition of *Pediatric Secrets* to his memory.

We are grateful to the chapter authors, many of whom have stayed with us through multiple editions, for their expertise and insight and timeliness despite having busy clinical responsibilities; to Kevin Travers, Kamatchi Madhavan, and the editorial staff at Elsevier for their careful assistance and kind flexibility with deadlines; and to our families—children and grandchildren (pictured)—and especially our wives, Helene Polin and Nina Ditmar, for their patience and encouragement and, despite our sometimes chaotic schedules, for always leaving the light on for us.

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TOP 100 SECRETS

1. Be certain to evaluate the hip when a patient presents with knee pain, as hip pathology (e.g., Legg-Calvé-Perthes disease, slipped capital femoral epiphysis) frequently masquerades as knee or distal thigh pain.
2. A term newborn who does not pass stool within 48 hours of life should be evaluated for possible Hirschsprung disease.
3. The single greatest cause of missed school hours in females is dysmenorrhea, but less than 15% of teenage girls with dysmenorrhea will seek medical care.
4. Presentation of stroke in children varies by age. Neonates and infants commonly present with seizures, whereas older children typically have acute hemiplegia.
5. A newborn has only 50% of the normal vitamin K–dependent cofactors. Unless vitamin K is given intramuscularly as part of recommended prophylaxis, these cofactors steadily decline during the first 3 days of life, which places the infant at risk for vitamin K deficiency bleeding.
6. Lyme disease course and response to therapy should not be followed by antibody titers, as there is continued secretion of antibodies by memory cells. Both IgM and IgG antibodies may remain positive for up to 10 to 20 years after microbial eradication.
7. Methemoglobinemia should always be considered when a patient presents with evidence of cyanosis without demonstrable respiratory or cardiac disease.
8. Although commonly done in the past as a "test of cure," follow-up urine cultures for a clinically improving patient $>$2 months of age are not indicated because the yield is extremely low ($<$0.5%) in a clinically well child.
9. Exclusive use of goat milk, especially without consumption of supplemental solid foods, makes infants susceptible to developing megaloblastic anemia, as goat milk contains very little folic acid compared with cow milk.
10. Most chlamydial genital infections in teenagers are asymptomatic (up to 80% in females and 75% in males).
11. The most common childhood-onset psychiatric disorder is one of various types of anxiety disorders, with a prevalence as high as one in three among adolescents, and 8% have severe impairment.
12. Intelligibility of speech increases by about 25% per year from 25% at age 1 year to 100% at age 4 years. Significantly delayed intelligibility should prompt hearing and language evaluation.
13. It is rare for an infant to develop congestive heart failure (CHF) from supraventricular tachycardia (SVT) in $<$24 hours. When SVT is present for 24 to 36 hours, about 20% develop CHF. At 48 hours, the number increases to 50%.
14. Gynecomastia—enlargement or swelling of breast tissue—occurs in as many as 60% to 70% of adolescent boys, with most having spontaneous resolution in 1 to 2 years, although 25% can have persistence $\geq$2 years.
15. Telogen effluvium, the most common cause of diffuse hair loss in children, develops 2 to 5 months after a stressful event (e.g., surgery, birth, large weight loss) and resolves gradually without therapy.
16. The "atopic march" is the phenomenon in which about one-half of infants with atopic dermatitis eventually develop asthma and two-thirds develop allergic rhinitis.
17. Hyperbilirubinemia generally is not an indication for the cessation of breastfeeding, but rather for increasing its frequency.
18. Individuals with Down syndrome have a 20-fold increased lifetime risk for leukemia, including a 50-fold higher risk for children during the first 4 years of life.
19. Because of the injury risks and no evidence that supports promotion of physical strength or development of the lower extremities, the American Academy of Pediatrics recommends a ban on the manufacture and sale of infant walkers.
20. The most common specific etiology diagnosed in pediatric patients with a non-respiratory systemic febrile illness after international travel is malaria. More than half of the world's population live in areas where malaria is endemic.
21. The most identifiable cause of microscopic hematuria is hypercalciuria, defined as elevated urinary calcium excretion without concomitant hypercalcemia.
22. IgA is the last immunoglobulin produced by a newborn, approaching 20% of adult values by 1 year of age, but not reaching adult values until adolescence. These physiologic delays in production make it difficult to diagnose IgA deficiency with any certainty in children $<$2 years.
23. About 6% of children are streptococcal carriers and will have positive throat cultures between episodes of pharyngitis.
24. Kawasaki disease is the most common cause of identifiable acquired heart disease in the developed world. The diagnosis should be considered in any child with a high fever lasting $>$5 days.
25. Sixty-five percent of children are born with one to four wisdom teeth (third molars), but the decision to prophylactically remove asymptomatic, disease-free wisdom teeth due to an increased risk for future complications is controversial.
26. Although hematuria ($>$2 red blood cells [RBCs]/high power field) is common in children with kidney stones, up to 15% may not have detectable hematuria.
27. Acne vulgaris that begins before age 7 years warrants further investigation for endocrine abnormalities such as androgen excess or precocious puberty.

28. In children with simple obesity (e.g., familial), linear growth is typically enhanced; in children with endocrinopathies (e.g., Cushing syndrome, hypothyroidism), linear growth is usually impaired.
29. The most common cause of persistent seizures in children is an inadequate serum antiepileptic level.
30. Genetic influences are strong in pediatric nocturnal enuresis. If both parents were enuretic, a child's likelihood is about 75%; if one parent was involved, the likelihood is about 50%.
31. During the first year of life, hypotonia is more common than hypertonia in infants who are ultimately diagnosed with cerebral palsy.
32. In patients with sickle cell disease, use of transcranial Doppler ultrasound to measure intracranial blood flow and regular transfusions to reduce the hemoglobin S content for those with abnormal values can significantly lower the likelihood of stroke.
33. In infants with significant gastroesophageal reflux, 25% to 50% spontaneously resolve by 6 months of age, 75% to 85% by 12 months of age, and 95% to 98% by 18 months of age.
34. When vaccinations are given as recommended in the anterior lateral thigh in an infant or in the deltoid muscle in toddlers $>$18 months, aspiration (which increases pain and time to administer) is not required because no large blood vessels are located at those preferred sites.
35. An infant with vomiting, lethargy, hypoglycemia, and no ketones on urinalysis should be evaluated for a fatty-acid oxidation defect.
36. Treatment failures are more common in osteomyelitis than in septic arthritis because antibiotic concentrations are much greater in joint fluid than in inflamed bone, devitalized bone may serve as an ongoing nidus for infection, and diagnosis of osteomyelitis is more likely to be delayed than diagnosis of septic arthritis.
37. Acute kidney injury (AKI) has replaced the term acute renal failure (ARF) to reflect the more appropriate concept that smaller reductions in kidney function (short of complete organ failure) have significant clinical repercussions in terms of morbidity and mortality.
38. An infant with nonsyndromic sensorineural hearing loss should be tested for mutations in the connexin 26 gene. Mutations in that gene contribute to at least 50% of autosomal recessive hearing loss and about 10% to 20% of all prelingual hearing loss.
39. Storage of urine specimens in room air prior to culture is one of the most common causes of false-positive culture results, as enteric organisms have a growth-doubling time of 12.5 hours in room air, which makes colony counts unreliable as a guide.
40. Women with primary genital herpes simplex virus (HSV) infections who are shedding HSV at delivery are 10 to 30 times more likely to transmit the virus than women with recurrent infection.
41. Be wary of midline facial dermoid cysts, as they carry an increased risk for intracranial connections.
42. Headaches that awaken children from sleep, are associated with vomiting without nausea, are made worse by straining or coughing, and have intensity changes with changes in body position are concerning for pathology that is causing increased intracranial pressure.
43. The most common genetic lethal disease, defined as a disease that interferes with a person's ability to reproduce as a result of early death or impaired sexual function, is cystic fibrosis.
44. About 10% to 20% of patients with Rocky Mountain spotted fever do not develop a rash, so a high index of suspicion is needed for any patient in an endemic area who presents with fever, myalgia, severe headaches, and vomiting.
45. In children or teenagers with a palpable solitary thyroid nodule, an aggressive diagnostic evaluation is needed because 20% to 25% will have a carcinoma.
46. Myocarditis should be suspected clinically when there is tachycardia out of proportion to fever, tachypnea, a quiet precordium, muffled heart tones, gallop rhythm without murmur, and hepatomegaly.
47. Adolescents with attention-deficit/hyperactivity disorder (ADHD), particularly those who are untreated, are at increased risk for high-risk behaviors, including higher rates of sexually transmitted infections (STIs), substance abuse, automobile accidents, and school problems (grade failure, dropping out, expulsion).
48. A male child with a liver abscess should be considered to have chronic granulomatous disease until proven otherwise.
49. Tumor lysis syndrome, an oncologic emergency of spontaneous or chemotherapy-induced massive breakdown of tumor cells, results in hyperuricemia, hyperphosphatemia, secondary hypocalcemia, and hyperkalemia, which increases the risk for sudden death.
50. Premature babies should be immunized in accordance with postnatal chronologic age.
51. Amenorrhea with unilateral abdominal or pelvic pain, irregular vaginal bleeding, and abdominal pain with a positive pregnancy test are indicative of ectopic pregnancy until proven otherwise.
52. Carbon monoxide poisoning is often misdiagnosed because the presenting symptoms can be flu-like.
53. Bilingual children develop speech milestones normally; two-language households should not be presumed as a cause of speech delay.
54. Because of the increased frequency of potential coexisting autoimmune conditions, children with type 1 diabetes mellitus should be screened for thyroid disorders and celiac disease soon after diagnosis.
55. After iron supplementation for iron-deficiency anemia, the reticulocyte count should double in 1 to 2 weeks, and hemoglobin should increase by 1 g/dL in 2 to 4 weeks. The most common reason for persistence of iron-deficiency anemia is poor compliance with supplementation.
56. A pop or snap sensation in the setting of acute knee injury is usually associated with an anterior cruciate ligament injury, a meniscal injury, and/or patellar subluxation.

57. The leading cause of fatalities related to inhalant abuse in adolescents are fatal arrhythmias, often from volatile hydrocarbons, which affect myocardial cell membranes. One in five adolescents who die in this setting are using inhalants for the first time.
58. A falling serum sodium concentration during diabetic ketoacidosis (DKA) treatment is worrisome because it indicates either inappropriate fluid management or the onset of syndrome of inappropriate antidiuretic hormone (SIADH) and can herald impending cerebral edema.
59. In the evaluation of children with constipation, the most important physical examination component is the rectal examination, because large amounts of stool in the rectal vault almost always indicate functional constipation.
60. Signs of clavicular fracture, the bone most commonly fractured during delivery, include asymmetric movement of the upper extremities, crying with passive motion of an upper extremity, and palpable crepitance over the clavicular region.
61. Most amblyopia is unilateral; vision testing solely with both eyes open is inadequate.
62. Crawling is one of the least valuable markers of development because there is enormous variability in the timing of crawling, and a significant percentage of normal infants never crawl before walking.
63. Polycystic ovarian syndrome, which affects up to 10% of reproductive-age women, should be suspected in overweight or obese teenagers with amenorrhea/oligomenorrhea and signs of hyperandrogenism (e.g., hirsutism, acne).
64. Separation of the umbilical cord occurs normally, on average, by 10 days of life (range: 3 to 45 days). Delayed separation can occur in patients with leukocyte adhesion deficiency type 1 (LAD1), a condition of impairment of leukocyte mobilization into extravascular sites.
65. Most umbilical hernias <0.5 cm spontaneously close before a patient is 2 years old. A hernia >2 cm may still close spontaneously, but it may take up to 6 years.
66. A teenager with delayed puberty and a poor sense of smell may have Kallmann syndrome, a defect in gonadotropin-releasing hormone, which is associated with maldevelopment of the olfactory lobes, resulting in anosmia or hyposmia.
67. Up to 20% of adolescents with menorrhagia may have a bleeding disorder, most commonly von Willebrand disease.
68. Without a booster after age 5 years, pertussis protection against infection is about 80% during the first 3 years after immunization, dropping to 50% after 4 to 7 years, and to near 0% after 11 years.
69. When acute gastrointestinal (GI) bleeding occurs in children, it may take 12 to 72 hours for full equilibration of a patient's hemoglobin to occur. Vital signs are much more useful for guiding patient management in the acute setting.
70. In girls' activities that emphasize leanness (e.g., gymnastics, ballet, diving), beware of the female athlete triad of menstrual dysfunction, low bone mineral density, and low energy availability (with or without disordered eating).
71. Three or more minor malformations should raise concern about the presence of a major malformation.
72. Up to 10% of normal, healthy children may have low-level (1:10) positive antinuclear antibody testing that will remain positive. Without clinical or laboratory features of the disease, it is of no significance.
73. An overweight 5-year-old is four times as likely to be an overweight teenager, which highlights the importance of addressing obesity at an early age.
74. The character of nasal secretions (e.g., purulent, discolored, tenacious) does not distinguish viral from bacterial causes, as mucopurulent rhinitis often accompanies the common cold. Early treatment (<7 to 10 days) of purulent nasal discharge is a common cause of antibiotic overuse.
75. The most common cause of chronic pelvic pain in adolescents without a history of pelvic inflammatory disease is endometriosis.
76. As an aid in the diagnosis and treatment of pneumonia, correlation between throat and nasopharyngeal bacterial cultures is poor and of limited value. Healthy children may be colonized with a wide variety of potentially pathogenic bacteria (an exception being *Bordetella pertussis*).
77. The most common clinical presentation of juvenile polyps in children is painless rectal bleeding, with up to one-third of patients having chronic blood loss with microcytic anemia.
78. Infants infected in the perinatal period with hepatitis B have a $>90\%$ chance of developing chronic hepatitis B infection, and of these, 25% go on to develop hepatocellular carcinoma.
79. Always consider ovarian torsion in the differential diagnosis of abdominal pain in girls, particularly during the ages of 9 to 14 years, when ovarian cysts as potential lead points are more common because of the maturing reproductive hormonal axis.
80. Basilar-type migraine, which occurs in up to 19% of childhood migraines, is likely in a child with a history of headaches, a family history of migraines, and presentation with a spinning sensation and double vision followed by an occipital headache.
81. Flexible flat feet, which occur in 15% to 20% of the pediatric population, can be distinguished from pathologic varieties of rigid flat feet by noting that when a child is sitting or standing on tiptoes, the arch gets bigger and looks normal.
82. Neonates with midline lumbosacral lesions (e.g., sacral pits, hypertrichosis, lipomas) above the gluteal crease should have screening imaging of the spine performed to search for occult spinal dysraphism.
83. A patient with Lyme disease or syphilis who develops fever, myalgias, and chills after starting antibiotic therapy likely has a Jarish-Herxheimer reaction, which is thought to be mediated by endotoxin release as the organism is destroyed. This may be mistaken for an allergic reaction to the antibiotic.
84. In children with esophageal food impaction, endoscopy and biopsy reveal an underlying pathologic and potentially treatable etiology in the majority of patients. In teenagers, the most common cause is eosinophilic esophagitis.

85. Syncope is more likely to be of a cardiac nature if there is sudden onset without prior dizziness or awareness, occurrence during exercise, history of palpitations before fainting, syncope results in an injury from a fall, and/or a positive family history of sudden death.
86. The best measure of cognitive function in a younger child is receptive language, which should be assessed in a fashion that is free of motor requirements.
87. Seizures with fever in patients >6 years of age should not be considered febrile seizures.
88. Cytomegalovirus is the most common congenital infection, up to 1.3% in some studies, but 80% to 90% of infected neonates are asymptomatic at birth or in early infancy.
89. Occasional strabismus is common in young infants because the macula and fovea are poorly developed at birth, but intervention should be considered for symptoms that persist beyond 2 to 3 months of age.
90. Unlike American Heart Association changes involving out-of-hospital resuscitation in adults, compression-only cardiopulmonary resuscitation (CPR) is not recommended for children, as ventilation remains vital for infants and children. Most pediatric arrests originate from a noncardiac nature with progressive tissue injury and hypoxia due to respiratory failure or shock.
91. A child with systemic juvenile idiopathic arthritis (JIA) who becomes ill with thrombocytopenia, profound anemia, and markedly elevated transaminases likely has macrophage activation syndrome, a complication involving massive upregulation of T-cell and macrophage function and vast release of proinflammatory cytokines with subsequent hemophagocytosis.
92. Because irreversible histologic changes can develop in 4 to 8 hours after the onset of testicular torsion, timely diagnosis is critical. Testicular salvage rates are <10% if symptom duration is 24 hours or more.
93. In a toddler with suspected idiopathic thrombocytopenic purpura (ITP), the presence of splenomegaly warrants more aggressive evaluation for an associated problem (e.g., collagen-vascular disease, hypersplenism, leukemia, glycogen storage disease).
94. Asthma rarely causes clubbing in children. Consider other diseases, particularly cystic fibrosis.
95. The optimal time frame for surgery for a patient with an undescended testicle is <12 months of age but not <6 months of age in order to optimize fertility potential and to decrease the risk for future testicular cancer. Spontaneous descent after 9 months is unlikely, and ultrastructural changes in the seminiferous tubules can occur in the second year of life.
96. A sexually active teenager with adnexal and right upper quadrant tenderness likely has Fitz-Hugh–Curtis syndrome, an infectious perihepatitis caused by gonococci or *Chlamydia* by direct spread from a pelvic infection along the pericolic gutters to the liver, which results in inflammation and capsular adhesions.
97. The most frequent cause of chronically elevated aminotransferases among children and adolescents in the United States is nonalcoholic fatty liver disease (NAFLD), which is commonly seen in obese patients with metabolic syndrome.
98. Nearly 100% of infants with chlamydial pneumonia are afebrile, and less than half have inclusion conjunctivitis.
99. Left shoulder pain after abdominal trauma is a worrisome sign that could represent blood accumulating under the diaphragm, which results in pain referred to the left shoulder (Kehr sign) due to splenic injury.
100. The most common worldwide cause of chronic gastrointestinal blood loss is hookworm infection, which is often associated with iron-deficiency anemia.

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CHAPTER 1

ADOLESCENT MEDICINE

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CLINICAL ISSUES

1. How does the "HEEADSSSS" mnemonic assist in adolescent interviewing?

This mnemonic allows for a systematic approach to the evaluation of multiple health issues and risk factors that affect teenagers:

- **H–Home** (living arrangement, family relationships, support)
- **E–Education** (school issues, study habits, achievement, expectations)
- **E–Eating** (healthy eating lifestyle, binge, purge, restricting, food security)
- **A–Activities** (recreation, friends, exercise, employment)
- **D–Drugs** (alcohol, tobacco, marijuana, cocaine, pills, etc.)
- **S–Sexuality** (sexual activity, sexual orientation)
- **S–Self-esteem** (body image)
- **S–Safety** (abuse, intimate partner violence, risk for self-harm)
- **S–Suicidality and depression**

2. How is *motivational interviewing* valuable when evaluating an adolescent?

Motivational interviewing is a set of patient-centered communication techniques focused on being empathetic, nonjudgmental, and supportive, which helps individuals express their own reasons for change and take responsibility for their own behavior. Some tools in your motivational interviewing toolkit include asking open-ended questions, reflective listening, sharing the agenda setting, eliciting pros and cons of change, providing information using the elicit–provide–elicit technique, inquiring about the importance and confidence of making a change, and summarizing the conversation.

AAP. Motivational Interviewing. www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/HALF-Implementation-Guide/communicating-with-families/Pages/Motivational-Interviewing.aspx. Accessed June 28, 2019.

3. What are the major health risks for adolescents worldwide?

- ***Early pregnancy and childbirth:*** The leading cause of death for 15- to 19-year-old girls globally is complications from pregnancy and childbirth.
- ***HIV and other infectious diseases:*** Although the overall number of deaths from HIV is decreasing, adolescent HIV-related deaths are rising. This may be due to more children with HIV surviving into adolescence.
- ***Mental health, violence, alcohol, tobacco, drugs, injuries, malnutrition, obesity, exercise, nutrition, and the rights of adolescents*** are other main issues affecting adolescents globally.

WHO. Adolescents: Health Risks and Solutions. https://www.who.int/news-room/fact-sheets/detail/adolescents-health-risks-and-solutions. Accessed June 28, 2019.

4. How does gun violence affect youth?

Gun violence affects children and youth in many ways: psychologically, emotionally, financially, and legally. But first and foremost, gun violence affects children's physical safety. In 2017, about 24% of males compared with 8% of females reported having carried a weapon (gun, knife, or club) on at least 1 day in the previous month.

Kann L, McManus T, Harris WA, et al. Youth risk behavior surveillance—United States, 2017, *MMWR.* 2018;67(8):1–114.

5. Which diagnoses require mandatory disclosure, regardless of confidentiality?

Most states require:

- Notification of child abuse to child welfare authorities under state child abuse (physical and sexual) reporting laws
- Notification of gunshot and stab wounds to law enforcement officials
- Warning from a psychotherapist to a reasonably identifiable victim of a patient's threat of violence
- Notification to parents or other authorities if a patient represents a reasonable threat to themselves (i.e., suicidal ideation)

6. Which teenagers <18 years can give consent for their medical care?

- Those who are <18 years old must be considered “emancipated” or “mature” minors to give consent for general medical care.
- Adolescents in some states can consent for health care needs related to substance abuse, mental health concerns, and sexual activity, including treatment of sexually transmitted infections (STIs), provision of contraceptive services, prenatal care, and abortion services. It is important for the clinician to note the significant variability among states in how the statutes are worded regarding access and confidentiality around providing these services.

Katz AL, Webb SA. Informed consent in decision-making in pediatric practice. *Pediatrics.* 2016;138(2):e20161485.

7. What is the difference between an emancipated and mature minor?

- A *mature minor* is an adolescent who has adequate maturity and capacity to understand and appreciate an intervention’s benefits, risks, likelihood of success, and alternatives. Under the mature minor doctrine, the age, overall maturity, cognitive abilities, and social situation of the minor are considered in whether they can provide their own consent for medical care.
- A legally *emancipated minor* is an adolescent who is living separately from his or her parents and is self-supporting, married, or on active duty with the armed forces. This does not specifically address decision-making ability, but rather the legal status of the minor.

Katz AL, Webb SA. Informed consent in decision-making in pediatric practice. *Pediatrics.* 2016;138(2):e20161485.

8. What is the difference between informed consent, assent, and informed refusal?

- *Informed consent* includes the following elements:
  - Necessary information provided by a medical provider
  - Medical understanding and the capacity of the decision-maker
  - A voluntary decision with the understanding of medical alternatives without undue influence, coercion, or manipulation
- *Assent* includes the following elements:
  - Helping a minor achieve a developmentally appropriate awareness of his or her condition
  - Telling the patient what he or she can expect with respect to tests and treatments
  - Clinically assessing the patient’s understanding of the situation (including whether there is inappropriate pressure to accept testing or therapy)
  - The patient’s willingness to accept the proposed care
- *Informed refusal* of life-sustaining, non–life-threatening, and nonurgent therapy by an adolescent should be given careful consideration. The physician and the family should try to understand the basis of the refusal and provide appropriate education for any misconceptions.

Katz AL, Webb SA: Informed consent in decision-making in pediatric practice. *Pediatrics.* 2016;138(2):e20161485.

9. What characterizes gender identity, gender expression, and gender dysphoria?

- *Gender identity* is how one identifies one’s own gender.
- *Gender expression* is the outward display of gender characteristics. This usually, but not always, conforms to anatomic sex.
- *Gender dysphoria* refers to the emotional stress of having a gender identity that is different from natal or anatomic sex.

10. What is the difference between gender identity and sexual orientation?

- *Gender identity* is a person’s internal feelings of being a woman, man, both, or neither. Most people have a gender identity and gender expression that match their sex assigned at birth. However, some people have a gender identity that is different from their sex assigned at birth; these people might use the term *transgender* or *gender nonconforming* to describe their gender identity.
- *Sexual orientation* refers to a pattern of sexual and romantic feelings for people of the same gender, a different gender, or more than one gender.

Young Men’s Health (YMH), Division of Adolescent and Young Adult Medicine at Boston Children’s Hospital. Sexual Orientation and Gender Identity: General Information. www.youngmenshealthsite.org/guides/sexual-orientation-gender-identity. Accessed June 28, 2019.

11. What health disparities are particular to LGBTQ youth?

LGBTQ (lesbian, gay, bisexual, transgender, queer/questioning) youth have higher rates of discrimination, family disapproval, social rejection, and violence. This may result in issues with self-esteem, depression, and suicidality. LGBTQ youth have also been found to have higher rates of drug and alcohol use, STIs (particularly HIV), and homelessness. Protective factors include family connectedness, caring adults, and school safety.

Kann L, McManus T, Harris WA, et al. Youth risk behavior surveillance—United States, 2017. *MMWR.* 2018;67(8):1–114.
Office of Disease Prevention and Health Promotion. www.healthypeople.gov/2020/topics-objectives/topic/lesbian-gay-bisexual-and-transgender-health. Accessed June 28, 2019.

12. What are some of the positive aspects of social media for adolescents?

Ninety-two percent of adolescents aged 13 to 17 go online daily, with 73% having access to a smartphone and 45% reporting daily use of social media at an average of 2 hours per day. Adolescents who use social media report increased self-confidence, self-esteem, reduced shyness, and less depression. Teenagers use social media, video chat, texting, and instant messaging to socialize, make plans, provide support, and collaborate on homework. Social media can support healthy behaviors such as daily exercise, accessing mental health services, and medication adherence through applications, games, and online social reinforcement and feedback. It can help improve social connectedness, emotional empathy, and moral sensitivity.

James C, Davis K, Charmaraman L, et al. Digital life and youth well-being, social connectedness, empathy, and narcissism. *Pediatrics.* 2017;140(Suppl 2):S71–S75.

13. What are some of the negative aspects of social media for adolescents?

Heavy media use is associated with diminished life satisfaction, internalizing negative experiences, depression, anxiety, attention problems, and stress. It can interfere with time spent with people face to face. Medical providers should discuss the value of creating digital curfews to increase health and well-being, particularly for younger youth or at-risk adolescents.

James C, Davis K, Charmaraman L, et al. Digital life and youth well-being, social connectedness, empathy, and narcissism. *Pediatrics.* 2017;140(Suppl 2):S71–S75.

14. What is cyberbullying?

Cyberbullying is using the Internet, cell phones, or social media venues to communicate false, embarrassing, or hostile information about someone else. This can range from insults to peer exclusion to sexual harassment. Cyber victims can develop emotional, behavioral, and school-related problems. Approximately 15% of students had been electronically bullied (counting being bullied through texting, Instagram, Facebook, or other social media) within the past year, with females more likely than males to be e-bullied.

Kann L, McManus T, Harris WA, et al. Youth risk behavior surveillance—United States, 2017. *MMWR.* 2018;67(8):1-114.
Suzuki K, Asaga R, Sourander A, et al. Cyberbullying and adolescent mental health. *Int J Adolesc Med Health.* 2012;24(1):27–35.

KEY POINTS: CLINICAL ISSUES

1. The adolescent medical interviewer should use the HEEADSSSS approach, as well as motivational interviewing, to engage and involve the adolescent in the health care visit.
2. Social media can have both positive and negative health effects for adolescents.
3. Gender identity and expression are a key developmental aspect of adolescents. LGBTQ youth may have specific health concerns and should be counseled accordingly.
4. Mandatory disclosure of diagnosis is required if child abuse is suspected, if gunshot or stab wounds are diagnosed, if a reasonable threat to a victim exists, or if patients represent reasonable threats to themselves.

EATING DISORDERS

15. How is the diagnosis of anorexia nervosa made?

Anorexia nervosa consists of a spectrum of psychological, behavioral, and medical abnormalities. The 2013 *Diagnostic and Statistical Manual of Mental* Disorders, Fifth Edition (DSM-5) lists three components needed for the diagnosis:

1. Restriction of energy intake relative to requirements, leading to a significantly low body weight—a weight that is less than minimally expected.
2. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though the affected individual is at a significantly low weight. Often, adolescents insist that they are trying to gain weight and are unable to do so, but their behaviors belie this contention.

3. Disturbances of perception of body shape and size, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

   The presence of amenorrhea is no longer necessary for the diagnosis of anorexia nervosa in postmenarchal girls.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

16. What are signs of anorexia nervosa on physical examination?

- Sinus bradycardia (or other dysrhythmias)
- Hypothermia
- Orthostatic changes in blood pressure and heart rate
- Dull, thinning hair
- Dry skin, lanugo (downy hair on body)
- Cachexia (especially facial wasting)
- Acrocyanosis (cold, bluish hands and feet)
- Extremity edema
- Heart murmur (mitral valve prolapse)
- Growth retardation
- Pubertal delay or arrest

17. Why are adolescent girls with anorexia nervosa at risk for low bone mineral density?

Significant weight loss affects the hypothalamic–pituitary axis, leading to suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This results in anovulation and subsequent low levels of serum estrogen. Because estrogen is necessary to incorporate calcium into bone, osteopenia may be a consequence.

18. What electrolyte disturbances can occur in patients with severe anorexia nervosa, and what are the potential clinical effects?

- **Hypokalemia**: Dysrhythmias, poor gut motility, skeletal muscle myopathy, nephropathy
- **Hypocalcemia**: Muscle spasm and tetany, stridor, seizures
- **Hyponatremia**: Seizures, coma, death
- **Hypomagnesemia**: Muscle cramps, weakness, irritability, psychosis, seizures, dysrhythmias
- **Hypophosphatemia**: Muscle weakness, paresthesia, central nervous system (CNS) disturbances (e.g., irritability, delirium, seizures)

Of note, many patients with anorexia nervosa (who are not simultaneously purging) have normal electrolytes upon presentation.

Westmoreland P, Krantz MJ, Mehler PS. Medical complications of anorexia nervosa and bulimia. *Am J Med.* 2016;129(1):30–37.

19. What are some indications for hospital admission for a patient with anorexia nervosa?

- Median body mass index (BMI) $\leq$75% for age and sex
- Dehydration
- Electrolyte abnormalities (e.g., hypokalemia, hyponatremia, hypophosphatemia)
- Cardiac dysrhythmia, electrocardiogram (ECG) abnormalities (prolonged QT interval, severe bradycardia)
- Heart rate $<$50 beats per minute during the day, $<$45 beats per minute overnight, or blood pressure $<$90/45 mm Hg
- Orthostatic changes in pulse ($>$20 beats per minute) or blood pressure ($>$20 mm Hg systolic, $>$10 mm Hg diastolic)
- Temperature $<$96°F (35.6°C)
- Acute food refusal
- Failure of outpatient management
- Uncontrollable bingeing and purging
- Acute medical complication of malnutrition (syncope, seizure, congestive heart failure, pancreatitis)
- Severe coexisting psychiatric disease (e.g., suicidality, psychosis)

Golden NH, Katzman DK, Sawyer SM, et al. Update on the medical management of eating disorders in adolescents. *J Adolesc Health.* 2015;56(4):370–375.

20. What are the primary biochemical features of the refeeding syndrome?

The *refeeding syndrome* is a potentially fatal process that results from fluid shifts and electrolyte abnormalities, which occurs when someone who has been chronically malnourished is refed, either orally or parenterally.

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- **Hypophosphatemia**. In starvation, total body phosphorus is depleted, although the serum phosphorus level usually remains normal because of adjustments in renal excretion. When carbohydrates are added through feeding, insulin is secreted, which stimulates anabolic protein synthesis and enhances the intracellular uptake of glucose, phosphate, and water. This can lead to significant extracellular hypophosphatemia. Because phosphate is needed for metabolic processes, potentially fatal cardiac, respiratory, and neurologic complications can ensue.
- **Hypokalemia** and **hypomagnesemia** also can occur as both potassium and magnesium are shifted intracellularly during refeeding.

Pulcini CD, Zettle S, Srinath A. Refeeding syndrome. *Pediatr Rev.* 2016;37(12):516–523.

21. What is the family-based therapy model for treating anorexia nervosa?

In this intervention initially used at the Maudsley Hospital in London, parents are told to treat anorexia like any other illness. They are asked to be responsible for feeding their adolescent and limiting other behaviors that may result in weight loss. After some weight gain is obtained, responsibility for feeding and eating gradually transitions back to the adolescent.

22. How is the diagnosis of bulimia nervosa made?

According to the DSM-5, bulimia nervosa is diagnosed when a person engages in the following:

- Recurrent episodes of binge eating (characterized by eating an abnormally large amount of food in a short period associated with a feeling of a lack of control)
- Recurrent inappropriate compensatory weight-loss behaviors (such as vomiting, laxative or diuretic abuse, fasting, or excessive exercising)
- These behaviors must occur at least once a week for a period of 3 months
- Self-evaluation is unduly influenced by body weight/shape
- These behaviors cannot occur exclusively in the context of anorexia nervosa

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American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

23. What are the medical complications of bulimia nervosa?

- **Electrolyte abnormalities**: Hypokalemia, hypochloremia, and metabolic alkalosis may occur. These metabolic disturbances can cause life-threatening cardiac arrhythmias.
- **Esophageal:** Acid reflux with esophagitis and (rarely) Mallory-Weiss tears may be found.
- **Central nervous system**: Neurotransmitters can be affected, thereby causing changes in the patient's perceptions of satiety.
- **Miscellaneous:** Tooth enamel erosion, salivary gland enlargement, cheilosis (inflammation of the corners of the mouth), and knuckle calluses (Russell sign, Fig. 1.1) are signs of recurrent vomiting.

Westmoreland P, Krantz MJ, Mehler PS. Medical complications of anorexia nervosa and bulimia. *Am J Med.* 2016;129(1):30–37.

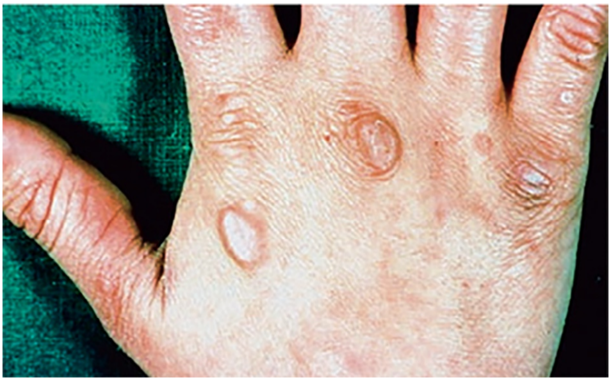

Fig. 1.1 Russell sign. Calluses on the knuckles arise from repeated contact with incisor teeth while inducing a gag reflex at the back of the throat. (From Aschheim KW, ed. *Esthetic Dentistry.* 3rd ed. Philadelphia, PA: Mosby Elsevier; 2015;547.)

24. What is binge eating disorder?

The DSM-5 has placed *binge eating disorder* in its own category. It can be diagnosed when a person has recurrent episodes of binge eating (at least weekly for 3 months) with consumption of large amounts of food in a short period accompanied by a feeling of loss of control. During these episodes, a person may eat much more rapidly than normal, eat until uncomfortably full, eat large amounts when not feeling physically hungry, eat alone because of embarrassment, and/or feel disgusted with oneself, depressed, or guilty afterward. Three of the preceding five characteristics are required for the DSM-5 diagnosis. Additionally, this binge eating must be accompanied by marked distress and cannot be associated with compensatory purging.

25. An 11-year-old with weight loss due to avoidance of food because of its sensory characteristics has what condition?

Avoidant/restrictive food intake disorder (ARFID). This is a more recently described type of eating disorder, distinct from anorexia nervosa or bulimia nervosa. Typically seen in children and younger teens, those with this disorder may avoid foods because of an aversion to some aspect of the food (color or texture) or because of a previous frightening experience associated with eating, such as choking or vomiting. The food restriction leads to weight loss, nutritional deficiencies, or interference with psychosocial functioning. Unlike in those with anorexia nervosa or bulimia, food avoidance is not influenced by body image.

Rome ES, Strandjord SE. Eating disorders. *Pediatr Rev.* 2016;37(8):323–336.

26. What modalities are used to treat eating disorders?

- A collaborative approach to care with a team consisting of a medical provider, a nutritionist, and a mental health professional is the ideal. Outpatient nutritional rehabilitation with monitoring is the preferred management for patients with milder disease. Family-based therapy is a first-line psychological treatment for adolescents with anorexia nervosa.
- Hospitalization with inpatient refeeding and monitoring may be necessary for unstable patients or for those who have failed outpatient therapy.
- Outpatient day treatment or inpatient residential treatment are also options for the treatment of those with more recalcitrant disorders.

Position Paper of the Society for Adolescent Health and Medicine. Medical management of restrictive eating disorders in adolescents and young adults. *J Adolesc Health.* 2015;56:121–125.

27. Name the three features that constitute the "female athlete triad."

This syndrome is also known as *RED-S* (Relative Energy Deficiency in Sports) and is comprised of the following: **Low energy availability** (with or without disordered eating), **menstrual dysfunction, and low bone mineral density**. This triad can present in active girls and young women, particularly in those who engage in sports that emphasize leanness, such as gymnastics, ballet, or diving. Diagnosis is based on history, physical examination, and laboratory evaluation. The basic laboratory workup should include a urine pregnancy test, thyroid-stimulating hormone, prolactin, FSH, LH, and estradiol. Evaluation for bone mineral density and vitamin D levels may be helpful. Ongoing counseling regarding eating behaviors and need for adequate weight gain is important. The use of oral contraceptives may give patients a false sense of security by inducing menses, but it has not been shown to increase bone mineral density.

Loveless MB. Female athlete triad. *Curr Opin Obstet Gynecol.* 2017;29(5):301–305.
Weiss Kelly AK, Hecht S. The female athlete triad. *Pediatrics.* 2016;137(6):e20160922.

KEY POINTS: EATING DISORDERS

1. Eating disorders put young people at risk for serious electrolyte disturbances, as well as for other physiologic, metabolic, and hormonal disturbances.
2. When treating a patient with anorexia nervosa on an inpatient unit, be on the lookout for fluid overload and monitor electrolytes to avoid refeeding syndrome.
3. The female athlete triad consists of low energy availability (with or without disordered eating), menstrual dysfunction, and low bone mineral density.
4. Treatment for a patient with an eating disorder is best done using a collaborative approach that involves a medical practitioner, a nutritionist, and a mental health professional.

MENSTRUAL DISORDERS

28. How do you define a normal menstrual cycle?

- **Interval:** Count from the first day of one period to the first day of the next period; normal range is from 21 to 45 days in adolescents
- **Duration:** 3 to 7 days

- **Quantity:** Average is about 30 mL per cycle; >80 mL of blood loss is considered excessive. Changing a blood-soaked pad or tampon every 1 to 2 hours, bleeding through clothing, and using more than six pads or tampons per day are signs of excessive bleeding.

ACOG Committee on Adolescent Health Care. ACOG Committee Opinion No. 651, December 2015: Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Obstet Gynecol.* 2015;126:e143–e146.

29. What is the difference between primary and secondary amenorrhea?

- *Primary amenorrhea* is the failure to achieve menarche by 15 years or no menses by 3 years after the development of secondary sex characteristics.
- *Secondary amenorrhea* is ≥3 months of amenorrhea after achievement of menarche.

30. What is the value of a progesterone challenge test in a patient with amenorrhea?

If bleeding ensues within 2 weeks after the administration of oral medroxyprogesterone (5 to 10 mg daily for 5 to 10 days), the test is positive. This indicates that the endometrium has been primed by estrogen and that the outflow tract is functioning. No response indicates hypothalamic–pituitary dysfunction, anatomic obstruction, or ovarian failure.

31. What are some of the causes of amenorrhea in adolescents?

Causes of amenorrhea in adolescents include pregnancy, contraceptive use, stress, chronic illness, iatrogenic (i.e., medications, chemotherapy), disordered eating (e.g., anorexia nervosa), female athlete triad, anatomic anomalies (e.g., imperforate hymen, vaginal septum, uterine or vaginal agenesis), and endocrine causes. Endocrine disorders that can result in amenorrhea include hypothalamic/pituitary dysfunction, ovarian pathology, thyroid abnormalities, adrenal abnormalities, androgen insensitivity syndrome, and polycystic ovarian syndrome (PCOS).

Jamieson MA. Disorders of menstruation in adolescent girls. *Pediatr Clin North Am.* 2015;62(4):943–961.

32. How do you define the different types of "rrhagias"?

- *Menorrhagia*: Large quantity of bleeding
- *Metrorrhagia*: Irregular interval bleeding
- *Menometrorrhagia*: Heavy and irregular bleeding

33. What is the differential diagnosis of heavy menstrual bleeding?

Heavy menstrual bleeding, also sometimes referred to as *abnormal uterine or vaginal bleeding,* was formerly called *dysfunctional uterine bleeding (DUB).* This is usually caused by anovulation secondary to an immature hypothalamic–pituitary–ovarian axis. However, the differential diagnosis also includes pregnancy (ectopic, miscarriage), bleeding disorders (such as von Willebrand disease, often with onset of first menstrual cycle and affecting about 1% of the population), pelvic infection (gonorrhea, chlamydia), foreign body/trauma, and endocrinopathies (PCOS, thyroid disease).

34. You see an 18-year-old female who comes to your office complaining of 10 days of heavy menstrual bleeding, including soaking through a pad every 2 hours and passing clots. What are key points in the assessment of this patient?

- *Vital signs*: Look for orthostatic hypotension, tachycardia
- *Physical examination*:
    - Skin for acne, hirsutism, striae consistent with PCOS
    - Petechiae/bruising suggestive of a bleeding disorder
    - Palpation of abdomen to evaluate for undetected pregnancy
    - If sexually active: pelvic/bimanual examination to examine for infection and pelvic inflammatory disease (PID)
- *Laboratory tests*: Complete blood count (assessing for anemia and platelet count), reticulocyte count, thyroid-stimulating hormone (TSH), and pregnancy test

35. What are two key clinical features that determine the urgency of management of abnormal uterine bleeding?

Hemoglobin concentration (evaluating for anemia) and **signs of orthostatic hypotension**. The more severe the clinical feature, the more urgent and aggressive the management must be, particularly in the setting of acute hemorrhage.

36. How should you treat a patient with heavy menstrual bleeding?

Treatment is based on the extent of bleeding and the patient's hemoglobin. First, it is important to stabilize the endometrium by giving estrogen (hemostasis) and progestin (for endometrial stability). This can be done by using a combined oral contraceptive pill/patch/ring, a progestin-only pill, a progestin-containing injection (such as depo-medroxyprogesterone acetate), or a progestin-containing intrauterine device. Iron replacement should be given. Consider a blood transfusion if the patient is hemodynamically unstable. An alternative is to use an antifibrinolytic agent such as tranexamic acid to prevent breakdown of blood clots, especially if the patient has a contraindication to estrogen-containing medication or has a known bleeding disorder.

37. You see a 16-year-old overweight female who reports having irregular periods, acne, and having to remove hair on her upper lip and chin. What is her most likely diagnosis?

PCOS, which can affect up to 10% of reproductive-age women, is the most likely diagnosis. Symptoms include amenorrhea/oligomenorrhea, hyperandrogenism (hirsutism, acne), overweight/obesity, and polycystic ovaries on ultrasound. Not all patients with PCOS will have all of these symptoms. Endocrine abnormalities may include insulin resistance (with elevated blood insulin levels), elevated LH/FSH ratios, and elevated free and total testosterone. It is important to rule out other causes of symptoms by obtaining dehydroepiandrosterone sulfate (DHEA-S) (marked elevation suggests a possible adrenal tumor), TSH, prolactin (elevation suggests a possible pituitary tumor), and a morning 17-hydroxyprogesterone (to rule out late-onset congenital adrenal hyperplasia). Long-term risks and sequelae of PCOS include infertility, endometrial cancer, metabolic syndrome, and diabetes.

38. How common is dysmenorrhea?

Up to 90% of adolescents are affected by primary dysmenorrhea (pain during menses). The condition remains the single greatest cause of missed school hours in females. However, less than 15% of teenage females with dysmenorrhea will seek medical care. Most cases are primary, but about 10% of patients with severe dysmenorrhea symptoms will have uterine or pelvic abnormalities, such as endometriosis.

De Sanctis V, Soliman A, Bernasconi S, et al. Primary dysmenorrhea in adolescents: prevalence, impact, and recent knowledge. *Pediatr Endocrinol Rev.* 2015;13(2):512–520.

39. Does dysmenorrhea occur more commonly in early or late adolescence?

Late adolescence. Dysmenorrhea occurs almost entirely with ovulatory cycles due to prostaglandin release. Menstrual periods shortly after the onset of menarche are usually anovulatory. With the establishment of more regular ovulatory cycles after 2 to 3 years, primary dysmenorrhea in late adolescence becomes more likely.

40. What is the difference between primary and secondary dysmenorrhea?

- *Primary dysmenorrhea*, also called *functional dysmenorrhea,* is pain in the absence of pelvic disease. This usually presents in the second to third year after menarche; occurs with ovulatory cycles due to prostaglandin release and uterine hyperactivity; and may be associated with nausea, vomiting, and/or diarrhea. Pain is usually in the lower abdomen, back, or upper thighs.
- *Secondary dysmenorrhea* is painful menses due to a pathologic process. This includes endometriosis (endometrial tissue outside the uterus), pelvic infections, intrauterine device (IUD)–related pain (specifically from the nonhormonal copper IUD), pregnancy (either pregnancy-related bleeding or complication such as miscarriage), and genital tract anomalies (especially if dysmenorrhea has been present since menarche).

Gray SH. Menstrual disorders. *Pediatr Rev.* 2013;34(1):6–17.

41. What two classes of medications are most commonly used for dysmenorrhea?

- **Nonsteroidal anti-inflammatory drugs (NSAIDs):** These limit local prostaglandin production. Naproxen or ibuprofen may be effective in up to 80% of patients.
- **Hormonal therapies:** Combined oral contraceptives act by reducing endometrial growth, which limits the total production of endometrial prostaglandin. Ovulation is suppressed, which also minimizes pain. Improvement may not be seen for up to 3 months.

Ryan SA. The treatment of dysmenorrhea. *Pediatr Clin North Am.* 2017;64(2):331–342.

42. What is a commonly underdiagnosed cause of chronic pelvic pain in adolescents without a history of PID?

Endometriosis. This condition results from the implantation of endometrial tissue in areas of the peritoneum outside the uterine cavity. It is reported in 25% to 38% of adolescents with chronic pelvic pain. The pain can be noncyclic (may occur with intercourse or defecation) or cyclic (often most severe just before menses, and dysmenorrhea is common). Studies show that endometriosis can be diagnosed in 50% to 70% of patients with dysmenorrhea who do not respond to NSAIDs. Definitive diagnosis is made by laparoscopy and biopsy. Therapy can be surgical (e.g., excision, coagulation, laser vaporization) and/or medical (e.g., gonadotropin-releasing hormone analogues, combination oral contraceptives, medroxyprogesterone acetate).

Stuparich MA, Donnellan NM, Sanfilippo JS. Endometriosis in the adolescent patient. *Semin Reprod Med.* 2017;35(1):102–109.
Matalliotakis M, Goulielmos GN, Matalliotakis C, et al. Endometriosis in adolescent and young girls: report on a series of 55 cases. *J Pediatr Adolesc Gynecol.* 2017;30(5):568–570.

KEY POINTS: MENSTRUAL DISORDERS

1. Consider von Willebrand disease for abnormally heavy bleeding at menarche or unusually long menstrual periods.
2. Always consider pregnancy in a patient with secondary amenorrhea.
3. Signs of androgen excess (hirsutism and/or acne) in the setting of menstrual irregularities suggest PCOS.
4. Ask about dysmenorrhea; it affects >50% of teenage girls and causes considerable school absence.
5. Consider endometriosis in any adolescent with chronic pelvic pain.

OBESITY

43. What are some of the health risk factors related to obesity?

A variety of physical, social, and emotional potential problems are involved (Fig. 1.2).

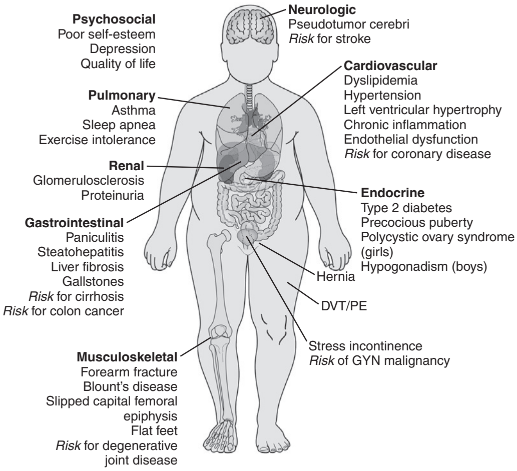
Psychosocial
Poor self-esteem
Depression
Quality of life
Pulmonary
Asthma
Sleep apnea
Exercise intolerance
Renal
Glomerulosclerosis
Proteinuria
Gastrointestinal
Paniculitis
Steatohepatitis
Liver fibrosis
Gallstones
Risk for cirrhosis
Risk for colon cancer
Musculoskeletal
Forearm fracture
Blount's disease
Slipped capital femoral epiphysis
Flat feet
Risk for degenerative joint disease
Neurologic
Pseudotumor cerebri
Risk for stroke
Cardiovascular
Dyslipidemia
Hypertension
Left ventricular hypertrophy
Chronic inflammation
Endothelial dysfunction
Risk for coronary disease
Endocrine
Type 2 diabetes
Precocious puberty
Polycystic ovary syndrome (girls)
Hypogonadism (boys)
Hernia
DVT/PE
Stress incontinence
Risk of GYN malignancy

Fig. 1.2 Complications of adolescent obesity. *DVT/PE,* Deep vein thrombosis/pulmonary embolism; *GYN,* gynecologic. (From Slap GB. *Adolescent Medicine: The Requisites in Pediatrics.* Philadelphia, PA: Elsevier Mosby; 2011:67.)

44. What variety of factors may contribute to obesity?

Both **genetic** and **environmental** factors are associated with obesity in most cases. Endocrine disorders and genetic syndromes leading to obesity are uncommon. An emerging area of interest is *epigenetics,* which is defined as the study of heritable changes in gene expression that occur without a change in the deoxyribonucleic acid (DNA) sequence. Epigenetic mechanisms would include alterations in DNA methylation, histone modifications, or other epigenetically related processes that might increase susceptibility to weight gain.

- **Genetic factors** may explain the variance of fat distribution and metabolism rate.
- **Genetic syndromes** include Prader-Willi, Cohen, and Bardet-Biedl syndromes and are rare.
- **Environmental factors** include increased caloric intake and decreased physical activity.
- **Psychological** disordered eating may result in obesity.
- **Endocrine** causes, such as hypothyroidism, Cushing syndrome, and growth hormone deficiency, are rare.

Greydanus DE, Agana M, Kamboj MK, et al. Pediatric obesity. *Dis Mon.* 2018;64(4):98–156.

Marinez JA, Milagro FI, Claycombe KJ, et al. Epigenetics in adipose tissue, obesity, weight loss and diabetes. *Adv Nutr.* 2014;5(1):71–81.

45. What features on physical examination are particularly important in the evaluation of the obese patient?

- Blood pressure (hypertension)
- Acanthosis nigricans (type 2 diabetes)
- Hirsutism (PCOS)
- Thyroid (goiter, possible hypothyroidism)
- Right upper quadrant (RUQ) tenderness (gallbladder disease)
- Striae (Cushing syndrome)
- Tonsils (hypertrophy; potential for obstructive sleep apnea)
- Facial dysmorphic features (evidence of genetic syndrome)
- Limited hip range of motion (slipped capital femoral epiphysis)
- Small hands and feet, cryptorchidism (Prader-Willi syndrome)
- Lower-leg bowing (Blount disea

46. What screening laboratory tests should be done for obese adolescents?

For children who are obese or severely obese, a basic laboratory evaluation to rule out the presence of obesity-related metabolic abnormalities should be considered. These would include:

- **Serum aminotransferases (aspartate transaminase [AST] and alanine transaminase [ALT]):** To assess for possible nonalcoholic fatty liver disease (NAFLD)
- **Fasting lipid profile**: Elevated triglycerides and reduced high-density lipoprotein (HDL) are highly suggestive of significant insulin resistance.
- **Complete blood count (CBC)**: Iron deficiency and iron-deficiency anemia are common in obese children.
- **Fasting glucose**: Sensitivity, however, is low to detect glucose intolerance. A standard oral glucose tolerance test should be considered for severe obesity, positive family history of type 2 diabetes, or when acanthosis nigricans is present.
- **Vitamin D level**: Deficiency is common in obese children.
- **Thyroid function tests**

  Other tests should be determined if comorbidities are suspected by history or examination.

47. How are obesity and sleep interconnected?

- Lack of sleep is associated with an increased risk for obesity, and with each hour of sleep lost, the odds of becoming obese increase. People who sleep fewer hours also seem to prefer eating foods that are higher in calories and carbohydrates, which can lead to overeating, weight gain, and obesity. Sleep helps maintain a healthy balance of the hormones that regulate hunger (ghrelin) or satiety (leptin). Insufficient sleep causes levels of ghrelin to increase and levels of leptin to decrease. Sleep also affects the body's response to insulin, and lack of sleep results in a higher-than-normal blood glucose level, increasing the risk for diabetes.
- Obesity can cause sleep apnea and therefore disrupted sleep patterns. Daytime sleepiness and fatigue are common complaints even among obese patients without sleep apnea.

Fatima Y, Doi SAR, Al Mamun A. Sleep problems in adolescence and overweight/obesity in young adults: is there a causal link? *Sleep Health.* 2018;4(2):154–159.

Beccuti G, Pannain S. Sleep and obesity. *Curr Opin Clin Nutr Metab Care.* 2011;14(4):402–412.

48. Why is a short obese 11-year-old potentially of more clinical concern than a tall obese 11-year-old?

Being overweight is associated with an advanced skeletal age in preadolescents and younger adolescents, and thus, increased height compared with nonobese peers. Therefore, you expect them to be taller. Short stature in an obese 11-year-old could be a sign of possible endocrine disease.

49. What are the main features of the metabolic syndrome?

Insulin resistance, **overweight and obesity**, **abnormal glucose metabolism**, **dyslipidemia**, and **hypertension**. Other disorders associated with metabolic syndrome include fatty liver, PCOS, and proinflammatory states. Prevention and management of this condition can be accomplished with lifestyle modifications, behavioral interventions, pharmacologic interventions, and surgical interventions as needed.

Nehus E, Mitsnefes M. Childhood obesity and the metabolic syndrome. *Pediatr Clin North Am.* 2019;66(1):31–43.

50. What are the diagnostic criteria for the metabolic syndrome?

For children $\geq$10 years, metabolic syndrome can be diagnosed by abdominal obesity (i.e., waist circumference percentiles $>$90%) and the presence of two or more other clinical features: triglycerides $>$150 mg/dL, HDL $<$40 mg/dL, blood pressure (BP) systolic $\geq$130/diastolic $\geq$85 mm Hg, and known type 2 diabetes or elevated glucose.

Magge SN, Goodman E, Armstrong SC. The metabolic syndrome in children and adolescents: shifting the focus to cardiometabolic risk factor clustering. *Pediatrics.* 2017;140(2):e20171603.

51. How would you discuss weight management with an adolescent?

- Motivational interviewing techniques have been shown to decrease body mass index (BMI) percentile. It is important to express empathy through reflective listening, develop discrepancy between goals and their current behavior, avoid argument and direct confrontation, and support self-efficacy and optimism.
- Assess current diet history, encourage healthy dietary practices, and identify problem areas and behaviors.
- Help the adolescent set small attainable goals.
- Discourage the use of food as reward/comfort and avoid emotional eating.
- Encourage physical activity.
- Encourage family mealtimes; involve the family to help modify behaviors and lifestyle, encourage healthy foods and drinks, avoid buying sweets and sugary drinks, and recommend at least five servings of fruits and vegetables per day.

- Limit screen time, including TV, video games, the Internet, and cell phone use when not related to school work, and discourage a TV in the teen's bedroom.

Resnicow K, Harris D, Wasserman R, et al. Advances in motivational interviewing for pediatric obesity: results of the brief motivational interviewing to reduce body mass index trial and future directions. *Pediatr Clin North Am.* 2016;63(3):539–562.
Daniels SR, Hassink SG, Committee on Nutrition. The role of the pediatrician in primary prevention of obesity. *Pediatrics.* 2015;136(1):e275–e292.

52. What are the indications for bariatric surgery in adolescents?

Surgery can be considered when adolescents:

- Have a BMI $\geq$35 kg/m^2 with a severe comorbid condition (i.e., type 2 diabetes mellitus, severe obstructive sleep apnea [OSA], pseudotumor cerebri, or severe steatohepatitis) or a BMI $>$40 kg/m^2 with mild comorbidities (i.e., mild OSA, hypertension, insulin resistance, dyslipidemia, impaired quality of life)
- Have a sexual maturity rating stage IV or V
- Have completed at least 95% of skeletal maturity (as determined by expected final adult height)
- Are able to understand diet and lifestyle changes after surgery
- Have evidence of mature decision-making, social support, and motivation to comply with preoperative and postoperative treatments

Many experts also recommend that the patient should have failed sustained organized efforts through lifestyle intervention to lose weight before surgical intervention. Assent from the adolescent should always be obtained separately from the parents to avoid coercion.

Khattab A, Sperling MA. Obesity in adolescents and youth: the case for and against bariatric surgery. *J Pediatr.* 2019;107(4):18–22.
Styne DM, Arslanian SA, Connor EL, et al. Pediatric obesity—assessment, treatment and prevention: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(3):709–757.

KEY POINTS: OBESITY

1. Obesity is the most common chronic condition in children.
2. With obesity and short stature, think thyroid abnormalities and evaluate TSH and T_4 levels.
3. Only 5% of obese children have an identifiable underlying pathologic cause.
4. If a child is at risk as a result of family history, the earlier the modifications (e.g., limiting television time, encouraging exercise, and healthy diet), the better.
5. When counseling overweight and obese adolescents, keep weight reduction or stabilization goals reasonable; if too unrealistic, discouragement and weight cycling are more likely.

SEXUAL DEVELOPMENT

53. What is Tanner staging for boys?

In 1969 and 1970, Dr. James Tanner categorized the progression of stages of puberty (Table 1.1). It is now commonly referred to as *sexual maturity rating (SMR)* staging of sexual development. Separate scales define staging for males based on pubic hair and genital appearance. Of note, the limitation of this rating system is that it relies only on visual inspection. Accurate staging requires palpation for assessment of testicular volume.

Table 1.1 Tanner Staging for Boys

STAGE	DESCRIPTION
Pubic Hair	
I	None
II	Countable; straight; increased pigmentation and length; primarily at base of penis
III	Darker; begins to curl; increased quantity
IV	Increased quantity; coarser texture; covers most of pubic area
V	Adult distribution; spread to medial thighs and lower abdomen
Genital Development	
I	Prepubertal
II	Testicular enlargement (>4 mL volume); slight rugation of scrotum
III	Further testicular enlargement; penile lengthening begins
IV	Testicular enlargement continues; increased rugation of scrotum; increased penile breadth
V	Adult

54. What is the normal progression of sexual development and growth for boys during puberty?

Nearly all boys begin puberty with testicular enlargement. This is followed in about 1 to 1.5 years by pubic hair and then about 12 months later by phallic enlargement. For boys, puberty lasts an average of 3.5 years and begins an average of 2 years later than it does in girls (Fig. 1.3).

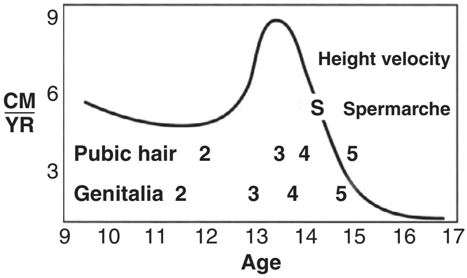

Fig. 1.3 Summary of pubertal development in boys. (From Rosen DS. Physiologic growth and development during adolescence. *Pediatr Rev.* 2004;25:194–200.)

55. What are the ranges of normal in the stages of pubertal development in girls?

Tanner divided pubertal development in girls according to pubic hair and breast development (Table 1.2).

Table 1.2 Tanner Stages for Girls

STAGE	DESCRIPTION
Pubic Hair	
I	None
II	Countable; straight; increased pigmentation and length; primarily on medial border of labia
III	Darker; begins to curl; increased quantity on mons pubis
IV	Increased quantity; coarser texture; labia and mons well covered
V	Adult distribution; with feminine triangle and spread to medial thighs
Breast Development	
I	Prepubertal
II	Breast bud present; increased areolar size
III	Further enlargement of breast; no secondary contour
IV	Areolar area forms secondary mound on breast contour
V	Mature; areolar area is part of breast contour; nipple projects

56. What is the normal progression of sexual development and growth for girls during puberty?

Most girls (around 85%) typically begin puberty with thelarche, or breast development. The appearance of breast buds may initially be asymmetric. Pubic hair usually starts to appear 1 to 1.5 years later, although this may occur first or simultaneously in some girls. In about 15% of girls, axillary hair may appear first. Menarche usually occurs about 18 to 24 months after the onset of breast development. For girls, the duration of puberty is about 4.5 years, which is longer than that for boys, which is around 3.5 years (Fig. 1.4).

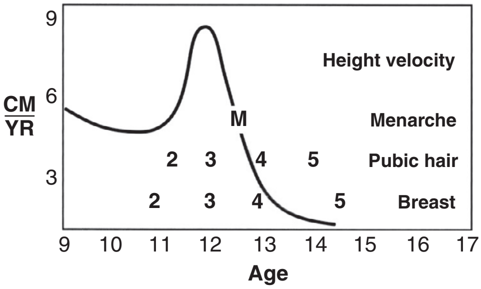

Fig. 1.4 Summary of pubertal development in girls. (From Rosen DS. Physiologic growth and development during adolescence. *Pediatr Rev.* 2004;25:198.)

57. What is the median age of menarche in the United States?

12.3 years. Non-Hispanic black females experience menarche slightly earlier than non-Hispanic white, Mexican American, and Asian females. Menstruation typically begins 2 to 2.5 years after breast development begins and occurs at SMR 3 to 4. Adolescent reports of menarche are highly correlated with parental reports.

Biro FM, Pajak A, Wolff MS, et al. Age of menarche in a longitudinal US cohort. *J Pediatr Adolesc Gynecol.* 2018;31(4):339-345.

Finer LB, Philbin JM. Trends in ages at key reproductive transitions in the United States, 1951-2010. *Women's Health Issues.* 2014;24(3): e271–e279.

58. Has the average age of menarche declined in the United States during the century?

According to the U.S. National Health and Nutrition Examination Surveys, there has not been a significant change in the median age at menarche over the past 30 years, except among the non-Hispanic black population, which has a 5.5-month earlier median age at menarche than it did 30 years ago. A higher BMI during childhood is related to an earlier onset of puberty.

59. How is delayed puberty defined for girls and boys?

- *In boys,* delayed puberty is defined as the absence of testicular enlargement ($>$4 mL) at an age that is 2 to 2.5 standard deviations later than the population mean. This has traditionally been defined as age 14 years in boys.
- *In girls,* delayed puberty is defined as the absence of breast development usually by age 13 years.

Wei C, Crowne EC. Recent advances in the understanding and management of delayed puberty. *Arch Dis Child.* 2016;101(5):481–488.

60. Why should the sense of smell be tested in a teenager with delayed puberty?

Kallmann syndrome is characterized by a defect in gonadotropin-releasing hormone (GnRH) with resultant gonadotropin deficiency and hypogonadism. Maldevelopment of the olfactory lobes also occurs, with resultant anosmia or hyposmia. Less commonly, cleft palate, congenital deafness, kidney malformation, pes cavus, and color blindness can co-occur. Boys who have GnRH deficiency often have a small phallus and testes, but physical examination may be significant only for sexual immaturity. Delayed bone age is the only consistent laboratory finding. These patients require hormonal therapy to achieve puberty and fertility.

61. What is the most common cause of delayed puberty?

Constitutional delay of growth and puberty (CDGP) is the cause of delayed puberty in 70% to 90% of cases, boys more commonly than girls. This is a form of hypogonadotropic hypogonadism in which there is delayed secretion of GnRH and activation of the gonadal axis. Fifty percent to 75% of children with CDGP have a family history of late-onset puberty, which indicates a strong genetic component. Children often are small for their age (less than fifth percentile) but have grown steadily. Bone age is delayed. Once puberty does begin, its progression is normal. Although it is considered a normal variant of growth, there are some consequences to adult height. Once the pubertal growth spurt occurs, its duration and the peak height velocity achieved are both reduced, resulting in a reduction in total pubertal height gain.

Graeme F. Growth disorders. In Martin M, Alderman E, Kreipe R, Rosenfeld W, eds. *Textbook of Adolescent Health Care.* Elk Grove Village, IL: American Academy of Pediatrics; 2011:656–666.

62. What features suggest constitutional delay of puberty?

- Family history of delayed puberty
- Short stature (boys are usually below the tenth percentile for height)
- Slowed growth velocity (4 to 5 cm/year in preadolescent girls and 3.5 to 4.5 cm/year in preadolescent boys) compared with same-age, same-sex peers (8 to 11 cm/year)
- Delayed bone age (from 1.5 to 4 years) compared with chronologic age; bone age is typically 12 to 13.5 years before the onset of puberty
- Normal prepubertal anatomy, sense of smell, and prepubertal LH and FSH levels

63. Which laboratory tests should you consider in a workup for delayed puberty?

If history or physical examination does not suggest an underlying cause, tests should include **LH**, **FSH**, **testosterone**, and **bone age**. These tests help categorize the condition as *hypergonadotropic* with increased GnRH, FSH, and LH (implying possible gonadal defects, androgen insensitivity, or enzyme defects) or *hypogonadotropic* with decreased GnRH and low to normal FSH and LH (implying constitutional delay or primary hypothalamic–pituitary problems). Most cases involve decreased GnRH.

64. What is the most common cause of primary gonadal failure in boys?

Klinefelter syndrome. The frequency of this condition is 1:1000 males. It is characterized in adolescence by gynecomastia and small, firm testes with seminiferous tubule dysgenesis. It is found in more than 80% of XXY males (i.e., males with 47 chromosomes). Onset of puberty is usually not delayed, and testosterone levels are usually adequate to initiate pubertal development. Levels of FSH and LH are elevated in these patients after the onset of puberty.

65. How do you evaluate a breast lump noted by a teenage girl on self-examination?

Although the incidence of cancerous lesions is extremely low in adolescents, breast lumps do require careful evaluation. Fibrocystic changes (i.e., the proliferation of stromal and epithelial elements, ductal dilation, cyst formation) are common in later adolescence and are characterized by variations in size and tenderness with menstrual periods. Cystic changes will often resolve over one to two menstrual cycles. Reassurance and observation should be provided. The most common tumor (70% to 95%) is a fibroadenoma, which is a firm, discrete, rubbery, smooth mass that is usually found laterally. This is the most surgically treated or biopsied mass in adolescents. Other causes of masses include lipomas, hematomas, abscesses, simple cysts, and, rarely, adenocarcinomas (especially if a bloody nipple discharge is present). The size, location, and other characteristics of a mass should be documented and reevaluated over the next one to three menstrual periods. A persistent or slowly growing mass should be evaluated with ultrasound, which can help distinguish cystic from solid masses. Mammography is a very poor tool for identifying distinct pathologic lesions in teenagers because the breast density of adolescents makes interpretation difficult.

Michala L, Tsigginou A, Zacharakis D, Dimitrakakis C. Breast disorders in adolescents: is there a need for a specialized service? *J Pediatr Adolesc Gynecol.* 2015;28(2):91–94.

KEY POINTS: SEXUAL DEVELOPMENT

1. If there are no signs of puberty by age 13 in girls and age 14 in boys, evaluate for an underlying medical cause.
2. Most cases of late puberty are constitutional delay.
3. Nearly all boys begin puberty with testicular enlargement; 85% of girls begin puberty with breast enlargement.
4. After onset, puberty lasts about 4.5 years for girls and 3.5 years for boys.
5. Mean time between the onset of breast development and menarche is around 18 to 24 months.

SEXUALLY TRANSMITTED INFECTIONS

66. Are adolescents more likely to get sexually transmitted infections (STIs) than adults?

Among sexually active people, adolescents have a **higher likelihood** than adults of being infected with an STI. About 25% of adolescents contract at least one STI by the time of high school graduation. About 40% of the annual incidence of chlamydia or gonorrhea infections occurs in previously infected teens. Many adolescents are reinfected within a few months of the index infection with the same organism. Reasons for the increased susceptibility in teens are biological, behavioral, and cultural:

- Cervical ectropion: *Neisseria gonorrhoeae* and *Chlamydia trachomatis* more readily infect columnar epithelium, and the adolescent ectocervix has more of this type of epithelium than does that of an adult.
- Cervical metaplasia in the transformation zone (from columnar to squamous epithelium) is more susceptible to human papillomavirus (HPV) infection.
- There is less frequent use of barrier methods of contraception among this population.
- Adolescents may have less access to quality STI prevention and management services for multiple reasons, including lack of insurance, school schedules, and concerns about confidentiality.

CDC. *Sexually Transmitted Diseases Surveillance 2017, STDs in Adolescents and Young Adults*. https://www.cdc.gov/std/stats16/adolescents.htm. Accessed June 27, 2019.

67. What are the Centers for Disease Control and Prevention (CDC) screening recommendations for STIs in adolescents?

For all sexually active females <25 years, the CDC recommends screening annually for chlamydia and gonorrhea. Universal screening for HIV (at least once) is recommended. Screening for syphilis and hepatitis B is on a case-by-case basis. Routine screening for other STIs such as trichomoniasis, herpes simplex virus (HSV), and HPV is not recommended. Risky sexual behaviors should determine screening frequency. Other populations, such as pregnant women, men who have sex with men (MSM), or HIV-infected adolescents, may require more thorough evaluation.

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(No. RR-137):1–137.

68. What is the best way to screen for STIs?

Nucleic acid amplification tests (NAATs), such as polymerase chain reaction or transcription-mediated amplification, are highly sensitive and specific, primarily for chlamydial and gonococcal infections. Advantages of NAATs include more rapid results and less invasiveness. Disadvantages include higher costs and lack of antibiotic sensitivity testing. NAATs are also the recommended testing method for rectal and oropharyngeal samples.

- NAATs can be performed on first-catch urine samples for both males and females or on specimen swabs collected from the endocervix or vagina in females (although vaginal specimens are preferred).

- NAATs used for vaginal swab specimens can be collected by a provider or self-collected in a clinical setting. Self-collected vaginal swabs are equivalent in sensitivity and specificity to those collected by a clinician. Self-collection has been found to be highly acceptable by women.
- The gold standard for STI diagnosis in cases of possible sexual abuse has traditionally been culture. However, according to American Academy of Pediatrics (AAP) guidelines, NAATs are preferable to culture to detect chlamydia and gonorrhea due to their high sensitivity and specificity (they are more likely to detect DNA before the end of the incubation period). The decision about which specific test is preferred may depend on the state. The CDC also recommends that NAATs can be performed on vaginal specimens to detect trichomonas.

Wiesenfeld HC. Screening for *Chlamydia trachomatis* infections in women. *N Engl J Med.* 2017;376(22):765–773.
Crawford-Jakubiak JE, Alderman EM, Leventhal JM. Care of the adolescent after an acute sexual assault. *Pediatrics.* 2017;139(3): e20164243.
Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(No. RR-137):51–68.

69. What are CDC treatment recommendations for common STIs?

See Table 1.3.

Table 1.3 CDC STI Treatment Guidelines

COMMON INFECTION	RECOMMENDED TREATMENT
Gonorrhea urethritis/cervicitis	Ceftriaxone 250 mg intramuscular (IM), single dose PLUS Azithromycin 1 g orally, single dose
Chlamydia urethritis/cervicitis	Azithromycin 1 g orally, single dose
PID	Ceftriaxone 250 mg IM, single dose PLUS Doxycycline 100 mg orally twice daily for 14 days **WITH or WITHOUT** Metronidazole 500 mg orally twice daily for 14 days PARENTERAL REGIMEN: Cefotetan 2 g IV every 12 hr OR Cefoxitin 2 g IV every 6 hr PLUS Doxycycline 100 mg oral or IV every 12 hr **OR** Clindamycin 900 mg IV every 8 hr PLUS Gentamycin (loading) 2 mg/kg IV once, followed by 1.5 mg/kg IV every 8 hr
Genital HSV	PRIMARY LESION: Acyclovir 400 mg orally three times a day for 7-10 days **OR** Valacyclovir 1 g orally twice a day for 7-10 days EPISODIC THERAPY FOR RECURRENT GENITAL HERPES: Acyclovir 800 mg orally twice a day for 5 days **OR** Valacyclovir 1 g orally once a day for 5 days SUPPRESSION: Acyclovir 400 mg orally twice a day **OR** Valacyclovir 1 g orally once a day (decrease to 500 mg once a day if <10 outbreaks/year)
Primary Syphilis	Benzathine penicillin G 2.4 million units IM in a single dose

HSV, Herpes simplex virus; *IM,* intramuscular; *IV,* intravenous; *PID,* pelvic inflammatory disease; *STI,* sexually transmitted infection.
Centers for Disease Control. https://www.cdc.gov/std/tg2015/default.htm. Accessed January 27, 2019.

70. What is the typical presentation of chlamydial genital infections in both female and male teenagers?

Most are **asymptomatic** (up to 80% in females and 75% in males), and infection can persist for several months. Those with asymptomatic infection contribute to the high rates of transmission, which is the reason for screening asymptomatic adolescents. In females with symptoms, chlamydia should be suspected if vaginal discharge and bleeding are noted, especially after intercourse. This may be due to endocervical friability. In males, the most typical symptoms are dysuria and a penile discharge, which is usually scant and watery or mucoid. Occasionally, penile itching or tingling may occur without discharge. Less frequently, urinary frequency, dysuria, hematuria, or hematospermia may occur.

Siqueira LM. Chlamydia infections in children and adolescents. *Pediatr Rev.* 2014;35(4);145–154.

71. What is the preferred treatment for chlamydial urogenital infections?

Either azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days. Both options have been proven to be efficacious with microbial cure rates of 97% and 98%, respectively. One should consider adherence issues and simplicity of administration in adolescents when choosing a regimen for treatment.

Geisler WM, Uniyal A, Lee JY, et al. Azithromycin versus doxycycline for urogenital Chlamydia trachomatis infection. *N Engl J Med.* 2015;373(26):2512–2521.

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(No. RR-137):1–137.

72. What is the typical appearance of *N. gonorrhoeae* on Gram stain?

Intracellular gram-negative diplococci (Fig. 1.5) are found on Gram stain.

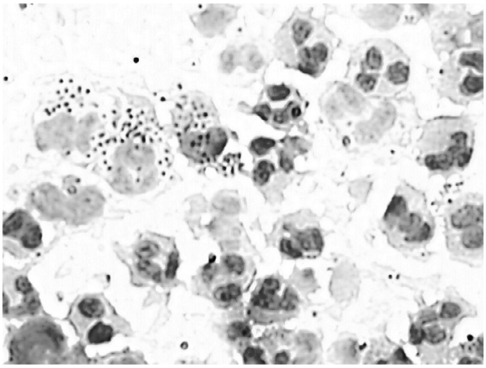

Fig. 1.5 Gram stain of *Neisseria gonorrhoeae*. (From Gates RH. *Infectious Disease Secrets.* 2nd ed. Philadelphia, PA: Hanley & Belfus; 2003:207.)

73. What is the reason for the use of two antibiotics for the treatment of sexually transmitted gonococcal infections in adolescents?

CDC recommendations for the treatment of gonorrhea infections includes dual treatment with intramuscular ceftriaxone and oral azithromycin, even if NAAT for chlamydia is negative. The purpose of dual treatment is to help prevent antimicrobial resistance, which can develop relatively quickly with *N. gonorrhea*. Combination therapy using two antimicrobials with different mechanisms of action is felt to improve treatment efficacy and to potentially slow the emergence of resistance to cephalosporins. During 2006–2011, it was found that cefixime was no longer an effective cephalosporin for the treatment of *N. gonorrhea,* and recommendations were changed for treatment with ceftriaxone.

CDC. *2015 Sexually Transmitted Diseases Treatment Guidelines*. https://www.cdc.gov/std/tg2015. Accessed June 27, 2019.

74. When is it recommended to retest for gonorrhea and/or chlamydia after treatment?

Repeat infections are most likely the result of reinfection caused by failure of the partner to get treated and not due to treatment failure, assuming compliance with therapy. Given the high prevalence of reinfection in both males and females who have had a previous gonorrhea or chlamydia infection in the preceding months, the CDC recommends that testing be repeated in 3 months after treatment, regardless of whether the patient believes that their sex partner was treated or not. Tests of cure 2 weeks after treatment, however, are recommended for those treated for pharyngeal gonorrhea with an alternative antibiotic regimen.

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(No. RR-137):1–137.

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75. What is expedited partner therapy?

Expedited partner therapy (EPT) is treating the patient's sexual partner(s) for presumed infection of gonorrhea or chlamydia without examining the partner(s) before dispensing treatment. The CDC has recommended this option to facilitate partner treatment. However, as the recommended treatment for gonorrhea is injectable ceftriaxone and oral azithromycin, an oral-only EPT regimen for gonorrhea can be considered only for heterosexual partners who are unlikely to seek treatment on their own. The legality of this practice is determined by each state.

Gannon-Loew KE, Holland-Hall C, Bonny CE. A review of expedited partner therapy for the management of sexually transmitted infections in adolescents. *J Pediatr Adolesc Gynecol.* 2017;30(3):341–348.

76. How are the three most common causes of vaginitis clinically distinguished?

- **Candidal vaginitis**: Vulvar itching, erythema and excoriations, vaginal discharge (thick, white, curdlike, lack of odor)
- **Trichomonal vaginitis:** Vulvar itching and soreness and erythema, vaginal discharge (gray, yellow-green, frothy; rarely malodorous)
- **Bacterial vaginosis**: Minimal erythema, vaginal discharge (malodorous fishy smell; thin white discharge clings to vaginal walls)

77. How does the vaginal pH help determine the cause of a vaginal discharge?

Ordinarily, the vaginal pH in a pubertal girl is <4.5 (compared with 7.0 in prepubertal girls). If the pH is >4.5, infection with trichomonas or bacterial vaginosis should be suspected.

78. How does evaluation of the vaginal discharge help identify the etiology?

See Table 1.4.

Table 1.4 Evaluation of Vaginal Discharge

	CANDIDAL VAGINITIS	TRICHOMONAL VAGINITIS	BACTERIAL VAGINOSIS
pH	≤4.5	>4.5	>4.5
KOH prep	Mycelia pseudohyphae	Normal	Fishy odor (positive "whiff" test)
NaCl prep	Few WBCs	Many WBCs; motile trichomonads	Clue cells

KOH, Potassium hydroxide; *NaCl,* sodium chloride (salt); *WBCs,* white blood cells.

79. How is trichomoniasis diagnosed?

Wet mount microscopy has been the most common method of diagnosis. For a wet mount, a sample of vaginal fluid is rolled onto a glass slide, and normal saline is added; look for the lashing flagella and jerky motility of the trichomonads (Fig. 1.6). Wet mounts, however, can be falsely negative in up to one-third of cases. *NAATs* are now available for detection of *Trichomonas vaginalis*, with higher sensitivities than the wet mount. There are now also point-of-care tests that use antigen-detection technology to detect trichomonas. These tests have lower sensitivity but comparable specificity to NAATs.

Territo HM, Wrotniak BH, Bouton S, Burstein GR. A new strategy for trichomonas testing female adolescents in the emergency department. *J Pediatr Adolesc Gynecol.* 2016;29(4):378–381.

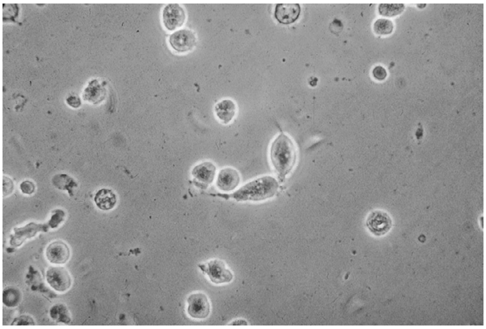

Fig. 1.6 Wet mount of vaginal secretions with leukocytes and flagellated trichomonads. (From Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia, PA: Churchill Livingstone; 2004;1361.)

80. “Clue cells” are clues to what condition?

Clue cells are vaginal squamous epithelial cells to which many bacteria are attached. This gives the cell a stippled appearance when viewed in a normal saline preparation (Fig. 1.7). Clue cells are characteristic, but not diagnostic, of **bacterial vaginosis**.

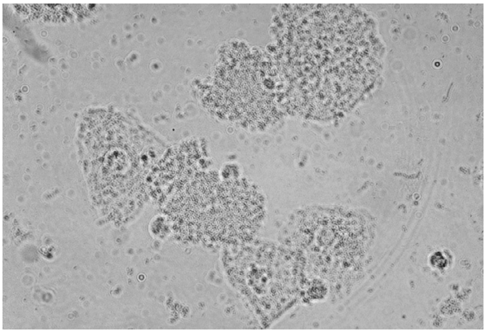

Fig. 1.7 “Clue cells” are squamous cells with folded cytoplasm and numerous bacteria (typically *Gardnerella vaginalis*) attached to their surface. (From Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases,* 6th ed. Philadelphia, PA: Churchill Livingstone; 2004:1366.)

81. What is the etiology of bacterial vaginosis?

Formerly called *nonspecific*, *Gardnerella*, or *Haemophilus vaginitis,* bacterial vaginosis is the replacement of normal vaginal lactobacilli with a variety of bacteria, including *Gardnerella vaginalis*, genital mycoplasmas, and an overgrowth of anaerobic species.

82. What are the criteria for the diagnosis of bacterial vaginosis?

Clinical diagnosis requires three of the four following criteria (Amsel criteria):

- Homogeneous thin, white or gray vaginal discharge
- Discharge pH >4.5
- On wet mount, >20% of cells are clue cells
- Positive “whiff” test: addition of 10% potassium hydroxide (KOH) to discharge results in fishy odor

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Patterson-Rose S, Braverman PK. Vaginitis and vaginosis. In Neinstein LS, ed. *Adolescent Health Care*, 6th ed. Philadelphia, PA: Wolters Kluwer; 2016:433–437.

83. If a patient is receiving a standard treatment for a trichomonal or bacterial vaginosis infection, why should alcohol be avoided?

The recommended treatment is **metronidazole**, which may interfere with the metabolism of ingested alcohol within 24 hours of dosing and may cause a disulfiram-like reaction in patients. (Disulfiram is a medication used to treat chronic alcoholism by inducing unpleasant effects when alcohol is consumed.) Symptoms may include abdominal pain, cramps, nausea/vomiting, facial flushing, and headaches.

84. Which STI is most closely linked to cervical cancer?

HPV. HPV affects 20% to 40% of sexually active adolescent females. More than 100 HPV types have been identified, of which about 30% are known to infect the genital tract. They differ in their clinical presentation. Types 6 and 11 classically cause 90% of genital warts. Types 16 and 18 cause the majority of cervical cancers. Because of this association, HPV vaccination is recommended by the Advisory Committee on Immunization Practices for boys and girls beginning at the 11- to 12-year visit, although vaccination can be given as early as age 9 years. Catch-up vaccination is also recommended for unvaccinated adolescents.

85. What are the manifestations of HPV infection?

HPV infection is typically **subclinical**, but infection can present with **anogenital condyloma acuminata** (genital warts). Cervical HPV infection may lead to cervical dysplasia and cervical cancer. Other complications may include vulvar and vaginal cancers. HPV is also a cause of nonsexually transmitted diseases, including deep **plantar warts**, **palmar warts**, and **common warts**. Cervical infection with both the low-risk and the high-risk types of HPV in adolescent girls often clears spontaneously over a 6- to 8-month period. In males, HPV infection has been associated with anal cancers, particularly among MSM and patients who are HIV infected. Oropharyngeal and penile cancers have also been associated with HPV infection.

86. When are Pap smears indicated in teenagers?

The American College of Obstetricians and Gynecologists recommends that routine cervical cytology screening (Pap smear) for healthy women begin at age 21. Only in certain circumstances (HIV infection, immunocompromised state) are Pap smears indicated in younger women. This is because most HPV infections in healthy adolescents self-resolve.

American College of Obstetricians and Gynecologists (ACOG). Screening for cervical cancer, ACOG Practice Bulletin Number 131. *Obstet Gynecol.* 2012;120:1222–1238.

87. Describe the appearance of condylomata acuminata.

Condyloma acuminata (anogenital warts) are soft, fleshy, polypoid or pedunculated papules that appear in the genital and perianal area. They may coalesce and take on a cauliflower-like appearance. Visualization of anogenital warts can be enhanced by wetting the area with 3% to 5% acetic acid (vinegar), which whitens the lesions. They may be located in the urethra or on the penis, scrotum, or perianal area of men and on the vulva, perineum, vagina, cervix, periurethral, or perianal area in women. They may also be found periorally.

88. What is the natural history of genital warts?

Left untreated, 40% of genital warts may spontaneously resolve, but the timing is unpredictable (months to years). The lesions are not oncogenic and will not progress to malignancy. Treatment, often done for cosmetic purposes or symptoms of itching or burning, consists of topical products, cryotherapy, or surgical removal. Recurrence can occur in as many as one-third of cases and usually manifests within the first 3 months after therapy.

89. What are the criteria for the diagnosis of PID?

Pelvic or lower abdominal pain without other likely cause and one or more of the following must be present:

- Uterine tenderness
- Cervical motion tenderness
- Adnexal tenderness

90. What additional criteria support the diagnosis of PID?

- Oral temperature $>$38.3°C (101°F)
- Abnormal cervical or vaginal discharge (with leukocytes $>$ epithelial cells)
- Elevated erythrocyte sedimentation rate (usually $>$15 mm/hr)
- Elevated C-reactive protein
- Cervical infection with *N. gonorrhoeae* or *C. trachomatis*

Because no single clinical aspect or laboratory test is definitive for PID, a constellation of findings is used to support the diagnosis. Of note, tests for gonorrhea and chlamydia are often negative in PID because although the disease is in the upper genital tract, specimens are typically obtained from the lower tract.

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(No. RR-137):1–137.

91. Which adolescents with PID should be hospitalized for intravenous antibiotics?

Those with any of the following conditions:

- Potential surgical emergency (if appendicitis or ectopic pregnancy cannot be excluded)
- Severe illness (e.g., overt peritonitis, vomiting, high fever)
- Tubo-ovarian abscess
- Pregnancy
- Immunodeficiency
- High suspicion for unreliable compliance or timely follow-up within 72 hours
- Failure of outpatient therapy

These are the same criteria that are used for older women when considering hospitalization for PID. No evidence is available that supports adolescents have better outcomes from hospitalizations for treatment for PID compared with adults if none of these conditions are present.

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(No. RR-137):1–137.

92. What are the common causative pathogens for PID?

PID is typically a polymicrobial ascending infection causing endometritis, salpingitis, and oophoritis. It is most commonly caused by **gonococcal or chlamydial** infections. Other pathogens include *Gardnerella* species, *Haemophilus influenza*, gram-negative rods, mycoplasma, *Ureaplasma urealyticum*, and cytomegalovirus.

93. A sexually active 17-year-old girl with adnexal and RUQ abdominal tenderness probably has what condition?

Fitz-Hugh–Curtis syndrome. This is an infectious perihepatitis that is caused by gonococci or by chlamydia. It should be suspected in any patient with PID who has RUQ tenderness. It may be mistaken for acute hepatitis or cholecystitis. The pathophysiology is thought to be the direct spread from a pelvic infection along the paracolic gutters to the liver, where inflammation develops and capsular adhesions form (the so-called *violin-string adhesions* seen on surgical exploration). If RUQ pain persists despite treatment for PID, ultrasonography should be done to rule out a perihepatic abscess.

Shikino K, Ikusaka M. Fitz-Hugh-Curtis syndrome. *BMJ Case Rep.* 2019;12(2):e229326.

94. What are the sequelae of PID?

Twenty-five percent of patients with a history of PID will have one or more major sequelae of the disease, including the following:

- Tubo-ovarian abscess
- Recurrent PID (about one in five patients)
- Chronic abdominal pain: May include exacerbated dysmenorrhea and dyspareunia related to pelvic adhesions in about 20% of patients with PID
- Ectopic pregnancy: Risk is increased 6- to 10-fold
- Infertility: Up to 21% after one episode of PID, 30% after two episodes, and 55% after three or more episodes

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Trent M, Haggerty CM, Jennings JJ, et al. Adverse adolescent reproductive health outcomes after pelvic inflammatory disease. *Arch Pediatr Adolesc Med.* 2011;165(1):49–54.

95. How are the genital ulcer syndromes differentiated?

Genital ulcers may be seen in herpes simplex, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale (donovanosis). Herpes and syphilis are the most common, and granuloma inguinale is very rare. Although there is overlap, clinical distinction is summarized in Table 1.5.

Table 1.5 Differentiation of Genital Ulcer Syndromes

	HERPES SIMPLEX	SYPHILIS (PRIMARY, SECONDARY)	CHANCROID	LYMPHOGRANULOMA VENEREUM
Agent	Herpes simplex virus	*Treponema pallidum*	*Haemophilus ducreyi*	*Chlamydia trachomatis*
Primary lesions	Vesicle	Papule	Papule-pustule	Papule-vesicle
Size (mm)	1-2	5-15	2-20	2-10
Number	Multiple, clusters (coalesce ±)	Single	Multiple (coalesce ±)	Single
Depth	Superficial	Superficial or deep	Deep	Superficial or deep
Base	Erythematous, nonpurulent	Sharp, indurated, nonpurulent	Ragged border, purulent, friable	Varies
Pain	Yes	No	Yes	No
Lymphadenopathy	Tender, bilateral	Nontender, bilateral	Tender, unilateral, may suppurate, unilocular fluctuance	Tender, unilateral, may suppurate, multilocular fluctuance

From Shafer MA. Sexually transmitted disease syndromes. In McAnarmey ER, Kreipe RE, Orr DP, et al, eds. *Textbook of Adolescent Medicine*. Philadelphia, PA: W.B. Saunders; 1992:708.

96. What are the main differences between HSV-1 and HSV-2?

Infections caused by HSV-1 and HSV-2 are common. HSV-1 is usually thought to infect the oropharynx, and HSV-2 is more likely to infect the genital tract, although both HSV-1 and HSV-2 can cause infection in either location. HSV-2 tends to cause most of the recurrent cases of genital herpes. HSV-1 is now being recognized as associated with an increasing proportion of cases of genital herpes, especially among young women and MSM.

Bradley H, Marowitz LE, Gibson T, et al. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999-2010. *J Infect Dis.* 2014;209(3):325–333.

97. How do recurrent episodes of genital herpes simplex infections compare with the primary episode?

- Usually less severe, with faster resolution
- Less likely to have prodromal symptoms (buttock, leg, or hip pain or tingling)
- Less likely to have neurologic complications (e.g., aseptic meningitis)

- More likely to have asymptomatic infections
- Duration of viral shedding is shorter (4 versus 11 days)

Bernstein DI, Bellamy AR, Hook EW 3rd, et al. Epidemiology, clinical presentation, and antibody response to primary infection with herpes simplex virus type 1 and type 2 in young women. *Clin Infect Dis.* 2013;56(3):344–351.

KEY POINTS: SEXUALLY TRANSMITTED INFECTIONS

1. Regardless of the pathogen, most STIs can be asymptomatic.
2. NAATs for chlamydia and gonorrhea are the preferred diagnostic tests when screening for STIs in males and females.
3. STI screening in girls is best done via vaginal swab or urine collection rather than through endocervical sampling. Self-collected vaginal swabs are acceptable in a clinical setting.
4. No single symptom, examination finding, or laboratory test is definitive for PID.
5. Cultures are often negative in PID because the disease is in the upper genital tract and specimens are obtained from the lower tract.

SUBSTANCE ABUSE

98. What categories of drugs are commonly abused by adolescents?

- **Sedative-hypnotics**: Alcohol, barbiturates, benzodiazepines, γ-hydroxybutyrate, flunitrazepam (Rohypnol), other sedatives
- **Stimulants:** Caffeine, cocaine, amphetamines, decongestants
- **Tobacco/nicotine:** Cigarettes, vaping, electronic cigarettes, hookahs, smokeless tobacco
- **Cannabinoids:** Marijuana, hashish, synthetic cannabinoids
- **Opioids**: Heroin, opium, pharmaceutical opioid painkillers, including methadone and oxycodone/oxycodone derivatives
- **Hallucinogens**: Lysergic acid diethylamide (LSD), phencyclidine, mescaline, psilocybin, hallucinogenic mushrooms, methylenedioxymethamphetamine (MDMA, ecstasy, Molly)
- **Inhalants**: Aliphatic, halogenated, and aromatic hydrocarbons; nitrous oxide; ketones; esters
- **Steroids**

99. What is the CRAFFT screen?

This is a six-item screening test for adolescent substance abuse. Two or more "yes" answers indicate with more than 90% sensitivity and more than 80% specificity potentially significant substance abuse. Several screening instruments are available for interviewing adolescents, and screening for alcohol or drug use should be part of routine medical care.

- **C**ar: Have you driven a car (or ridden with a driver) under the influence of drugs or alcohol?
- **R**elax: Do you use drugs or alcohol to relax, feel better, or fit in?
- **A**lone: Do you use drugs or alcohol while you are alone?
- **F**orget: Do you sometimes forget what you did while using drugs or alcohol?
- **F**amily/Friends: Do they ever tell you to cut down on drug or alcohol use?
- **T**rouble: Have you gotten into trouble when using drugs or alcohol?

Levy S, Williams J. Substance use screening, brief intervention, and referral to treatment. *Pediatrics.* 2016;138(1):e20161211.

100. What are characteristic physical signs of illicit drug use?

See Table 1.6.

Table 1.6 Physical Signs of Illicit Drug Use

PHYSICAL SIGN	DRUG OF ABUSE
Hypothermia	Phencyclidine, ketamine
Hyperthermia	Mescaline, LSD
Increased heart rate	Amphetamine, cocaine, marijuana, MDMA, LSD
Increased blood pressure	Amphetamine, cocaine, phencyclidine, MDMA, LSD
Decreased gag reflex	Heroin, morphine, oxycodone, other opiates, benzodiazepines
Conjunctival redness	Marijuana

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Table 1.6 Physical Signs of Illicit Drug Use (*Continued*)

PHYSICAL SIGN	DRUG OF ABUSE
Pinpoint pupils	Heroin, morphine, oxycodone, other opiates
Sluggish pupillary response	Barbiturates
Irritation/ulceration of nasal mucosa	Intranasal cocaine, heroin, inhalants
Oral sores/burns, perioral pyodermas	Inhalants
Cutaneous scars (“tracks”)	Intravenous use
Gynecomastia, small testes	Marijuana
Subcutaneous fat necrosis	Intravenous and intradermal use
Tattoos in antecubital fossa	Intravenous use
Skin abscesses and cellulitis	Intravenous and intradermal use

LSD, Lysergic acid diethylamide; *MDMA,* methylenedioxymethamphetamine.

101. Should an adolescent be screened for drug abuse without their consent?

The AAP advises against involuntarily drug testing of adolescents. The AAP recommends that pediatricians discuss who will receive results with adolescents and their parents before ordering a drug test. Others have argued that a teenager’s right to privacy and confidentiality does not supersede potential risks for serious damage from drug abuse, particularly if there is strong clinical suspicion or parental concern. Drug screening may be obtained without consent in cases of emergency where the minor is unable to give consent and/or the course of management may be dependent on the drug screen results. The legal ramifications are evolving and vary from state to state. In 1995, the U.S. Supreme Court ruled that random drug testing of high school athletes and participants in extracurricular activities is legal.

Levy S, Schizer M; Committee on Substance Abuse. Adolescent drug testing policies in schools. *Pediatrics.* 2015;135(4):1107–1112.
Levy S, Siqueira LM; Committee on Substance Abuse. Testing for drugs of abuse in children and adolescents. *Pediatrics.* 2014;133(6): e1798–e1807.

102. How long do illicit drugs remain detectable in urine specimens?

There is variability depending on a patient’s hydration status and method of intake, but, as a rule, metabolites can be detected after ingestion, as shown in Table 1.7. Most urine screens are very sensitive and may detect drugs up to 99% of the time in concentrations established as analytic cutoff points. However, the screens can be much less specific, sometimes with false-positive rates of up to 35%. Therefore, second tests using the analytic methodology most specific for the suspected drug should be used. Furthermore, the use of urine drug screening is of limited value because many drugs are not included in screening panels.

Levy S, Siqueira LM; Committee on Substance Abuse. Testing for drugs of abuse in children and adolescents. *Pediatrics.* 2014;133(6): e1803.

Table 1.7 Detection of Illicit Drug Metabolites

Alcohol	7-12 hours
Amphetamines	1-3 days
Barbiturates (short acting)	4-6 days
Benzodiazepines (short acting)	1 day
Cocaine	1-3 days
Heroin	$<$24 hours up to 1-2 days
Marijuana	1-3 days for single use; 3-5 weeks after last use for chronic smoker
Methadone	1-7 days
Morphine	1-2 days
Oxycodone	2-4 days
Phencyclidine	2-8 days for casual use; several weeks for chronic use

103. What are individual risk factors for alcohol abuse?

Risk factors include poor school performance, conduct disorder, and untreated attention-deficit/hyperactivity disorder (ADHD). Mood disorders and psychiatric conditions such as anxiety, depression, schizophrenia, and bulimia tend to co-occur with alcohol abuse. There may also be a genetic predisposition for substance abuse. A male child of an alcoholic father is five times more likely to become an alcoholic than a child with a nonalcoholic father. Twin studies have demonstrated heritability patterns to be between 50% and 75%.

104. Which type of substance abuse is more common in younger adolescents than older adolescents?

Inhalant abuse. These substances are used at a higher rate among 12- to 13-year-olds compared with older adolescents. Household products are typically abused, including aliphatic hydrocarbons (e.g., gasoline, butane in cigarette lighters), aromatic hydrocarbons (e.g., benzene and toluene in glues, acrylic paints, and permanent marking pens), alkyl halides (e.g., methylene chloride and trichloroethylene in paint thinners and spot removers), and ketones (e.g., acetone in nail polish remover). Inhalants are the first illicit drugs used in about 6% of adolescents. Marijuana and pain relievers are the next most common drug types to be used for the first time by adolescents. Inhalants have short durations of action and usually cannot be detected by toxicology screen.

Nguyen J, O'Brien C, Schapp S. Adolescent inhalant use prevention, assessment, and treatment: a literature synthesis. *Int J Drug Policy.* 2016;31:15–24.

105. What is the leading cause of fatality related to inhalant abuse?

Fatal arrhythmias. The volatile hydrocarbons sensitize the myocardium and cause depolarization of the myocardial cell membranes. Abnormal propagation of impulses can occur, sometimes associated with adrenaline surge (as when hallucinating or running from an authority figure), resulting in fatal arrhythmias. In adolescents who die from this entity, about one in five is using inhalants for the first time. This phenomenon may be referred to as *sudden sniffing death syndrome*. Other mechanisms for inhalant-related fatalities can involve asphyxiation, suffocation, convulsions or seizures, coma, or choking.

Tormoehlen LM, Tekulve KJ, Nañagas KA. Hydrocarbon toxicity: a review. *Clin Toxicol* (Phila). 2014;52(5):479–489.

106. What are the potential acute toxicities of marijuana use?

Acute toxicities include:

- Euphoria, perceptual problems (time, color, and space), intensification of ordinary sensory experiences
- Impairment of learning, memory, attention, and working memory
- Conjunctivitis/eye redness
- Abdominal pain, vomiting
- Tachycardia, postural hypotension
- Myoclonic jerking/hyperkinesis, ataxia, slurred speech, and motor impairment
- Respiratory depression (with a range of severity) and acute bronchospasm
- Psychiatric symptoms, including panic attacks, paranoia, and acute psychosis

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Blohm E, Sell P, Neavyn M. Cannabinoid toxicity in pediatrics. *Curr Opin Pediatr.* 2019;31(2):256–261.
Dowd MD. Acute marijuana toxicity in children. *Pediatr Ann.* 2018;47(12):e474–e476.

107. What are the potential toxicities of chronic marijuana use?

- **Pulmonary:** Decreased pulmonary function. Compared with cigarette smoke, marijuana smoke contains more carcinogens and respiratory irritants and produces higher carboxyhemoglobin levels and greater tar deposition. Studies have demonstrated premalignant changes in those who smoke marijuana but not tobacco. The long-term significance of this has not yet been determined. Chronic use is associated with symptoms of chronic bronchitis.
- **Gastrointestinal:** Cannabinoid hyperemesis syndrome. This is a syndrome of recurrent episodes of abdominal pain and intense nausea and vomiting, commonly relieved by hot showers.
- **Endocrine:** Decreased sperm count and motility in boys. Marijuana use may interfere with hypothalamic–pituitary function and increase the likelihood of anovulation in girls. Chronic use also antagonizes insulin, which may affect diabetic management. Marijuana use may also impair cortisol and growth hormone secretion, but the clinical implications are not yet known.
- **Neurologic/behavioral:** Diminished short-term memory, concentration, and ability for complex decision-making. Reaction time and motor coordination may be affected as well. There may also be interference with learning, possible "amotivational syndrome." Use early in adolescence may alter brain development and result

in cognitive impairment. Regular use is associated with an increased risk for anxiety and depression (although causality has not been established).

Biohm E, Sell P, Neavyn M. Cannabinoid toxicity in pediatrics. *Curr Opin Pediatr.* 2019;31(2):256–261.
Volkow ND, Swanson JM, Evins AE, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA Psychiatry.* 2016;73(3):292–297.
Schrot RJ, Hubbard JR. Cannabinoids: medical implications. *Ann Med.* 2016;48(3):128–141.

108. Can you experience withdrawal from marijuana?

Yes. Withdrawal symptoms include irritability, trouble sleeping, decreased appetite, and anxiety.

109. Is synthetic marijuana dangerous?

Synthetic marijuana (also called *synthetic cannabinoids*) is sold over the counter and not easily regulated by the Drug Enforcement Administration (DEA), as producers often tweak the chemical formula to avoid legal control. These drugs usually contain some herbal materials sprayed with designer chemicals that fall into the cannabinoid family and act on tetrahydrocannabinol (THC) receptors. They are dangerous because they are addictive; unregulated, active ingredients keep changing; and effects are unpredictable. They are sold in brightly colored foil packages or plastic bottles to attract consumers. In 2017, the CDC posted warnings about reports of severe bleeding and death resulting from contaminated synthetic cannabinoids. Other severe toxicities include rapid heart rate, vomiting, agitation, confusion, and hallucinations.

LeBoisselier R, Alexandre J, Lelong-Boulouard V, Debruyne D. Focus on cannabinoids and synthetic cannabinoids. *Clin Pharmacol Ther.* 2017;101(2):220–229.

110. When does cigarette smoking begin?

In the United States, about three-fourths of daily adult smokers started smoking when they were between the ages of 13 and 17 years. Nearly 9 out of 10 smokers begin by age 18 years. Cigarette smoking remains the major preventable cause of premature death in the world. In the United States, rates for teenagers <18 years have been declining since the late 1990s.

111. What are the 5 “A’s” of smoking cessation counseling?

1. **A**sk about tobacco use
2. **A**dvise to quit
3. **A**ssess willingness to attempt quitting
4. **A**ssist in attempt to quit (e.g., pharmacotherapy such as nicotine gum or patch)
5. **A**rrange follow-up

Brief smoking counseling regarding initiation, cessation, or prevention of relapse can be effective in as little as 3 minutes.

Pbert L, Farber H, Horn K, et al. State-of-the-art office-based interventions to eliminate youth tobacco use: The past decade. *Pediatrics.* 2015;135(4):734–747.

112. Which method of ingesting substances is dramatically on the rise among 13- to 17-year-olds?

E-cigarettes, also called “*vapes*” and “e-*pens*,” are devices that most commonly heat liquid substances that may contain nicotine (derived from tobacco), THC, cannabinoid oils (CBD), flavorings, and other additives to create an aerosol that is inhaled, a process known as *vaping*. Adolescent vaping has increased annually in contrast to cigarette smoking, which has continued to decline among adolescents and is at historic lows since it was first measured in 1991. This may be due to attitudinal changes, increased expense of tobacco products, and disapproval of smoking cigarettes from the negative publicity aimed at the tobacco industry in the 1990s.

Centers for Disease Control and Prevention (CDC). *Outbreak of Lung Injury Associated with the Use of E-cigarettes or Vaping Products*. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed January 22, 2020.
Johnston LD, Miech RA, O’Malley PM, et al. *Monitoring the Future National Survey Results on Drug Use: 1975-2017: Overview, Key Findings on Adolescent Drug Use.* Ann Arbor, MI: Institute for Social Research, The University of Michigan; 2018;43.

113. What are the risks Vaping?

Data regarding the safety, particularly with long-term consumption, of e-cigarettes and pens for the inhalation of THC have not caught up with the widespread use of these products. Serious toxicity has been identified as e-cigarette or vaping associated lung injury (EVALI) associated with the inhalation of vitamin E acetate found in THC containing e-cigarettes. This has caused severe lung disease requiring hospitalization and potentially resulting in death. Other serious adverse events are mostly related to the device itself with overheating, fires, and explosions. Minor side effects include mouth and throat irritation, cough, lightheadedness, and nausea. Major concerns for adolescents are the potential of inducing long-term nicotine dependence and increasing the acceptability and appeal of cigarette smoking.

Centers for Disease Control and Prevention (CDC). *Outbreak of Lung Injury Associated with the Use of E-cigarettes or Vaping Products.* https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed January 22, 2020.

Livingston CJ, Freeman RJ, Costales VC, et al. Electronic nicotine delivery systems or E-cigarettes: American College of Preventive Medicine's practice statement. *Am J Prev Med.* 2019;56(1):167–178.

114. What are the risks of smokeless tobacco?

Smokeless tobacco comes in three main forms: snuff (finely ground either loose or in packets), chewing tobacco, and snus (rhymes with "goose"; dissolvable tobacco).

As a result of the decreased gingival blood flow caused by nicotine, chronic ischemia and necrosis can occur. Chronic use results in gingival recession and inflammation, periodontal disease, and oral leukoplakia (a premalignant change). The risk for oral and pharyngeal cancer is increased. Smokeless tobacco, like cigarettes, is addictive.

Johnston LD, Miech RA, O'Malley PM, et al. *Monitoring the Future National Survey Results on Drug Use: 1975-2017: Overview, Key Findings on Adolescent Drug Use.* Ann Arbor, MI: Institute for Social Research, The University of Michigan; 2018;41.

115. What performance-enhancing drugs (PEDs) are used by teenagers?

The different classes of these drugs include **anabolic-androgenic steroids** (e.g., androstenedione), **growth hormone**, **stimulants**, **erythropoiesis-stimulating agents**, **nutritional supplements** (e.g., creatine, protein shakes), and **stimulants** (e.g., ephedrine, caffeine, or guarana). In general, PEDs do not produce significant gains over those seen with the onset of puberty. Risks include high rates of contamination and correlation with the future use of anabolic androgenic steroids. The AAP strongly denounces their use.

White N, Noeun J. Performance-enhancing drug use in adolescence. *Am J Lifestyle Med.* 2016;11(2):122–124.

LaBotz M, Griesemer BA. Use of performance-enhancing substances. *Pediatrics.* 2016;138(1):e1–e12.

116. What are the potential side effects of anabolic steroids?

See Table 1.8.

Table 1.8 Potential Side Effects of Anabolic Steroids

Endocrine	In males—testicular atrophy, oligospermia, gynecomastia
	In females—amenorrhea, breast atrophy, clitoromegaly
Musculoskeletal	Premature epiphyseal closure
Dermatologic	Acne, hirsutism, striae, male-pattern baldness
Hepatic	Impaired excretory function with cholestatic jaundice, elevated liver function test results, peliosis hepatis (a form of hepatitis in which hepatic lobules have microscopic pools of blood), benign and malignant tumors
Cardiovascular	Hypertension, decreased high-density lipoprotein, thrombosis
Psychological	Aggressive behavior, mood swings, depression

117. What are the clinical features of an opioid overdose?

An opioid overdose can be identified by a combination of three signs and symptoms referred to as the *opioid overdose triad.* The triad is **pinpoint pupils, unconsciousness**, and **respiratory depression**. Because of the respiratory depression, opioids are responsible for a high proportion of fatal drug overdoses around the world.

Sharma B, Bruner A, Barnett G, Fishman MD. Opioid use disorders. *Child Adolesc Psychiatr Clin N Am.* 2016;25(3):473–487.

118. What medication should be used in an opioid overdose emergency?

Naloxone (Narcan) is an opioid receptor antagonist and serves as an antidote to opioid overdose. It can be administered by multiple routes: intramuscularly (IM), intravenously (IV), subcutaneously (SQ), nasally, or endotracheally. Naloxone will displace the bound opioids from the opiate receptors, which will reverse the overdose and restore normal respiration. Opiate withdrawal can be precipitated, but this is primarily in chronic abusers.

119. What chronic maintenance medications can be used to prevent opioid addiction and relapse?

- **Buprenorphine** is a synthetic opioid that is a partial agonist at opioid receptors. It does not produce the euphoria and sedation and is able to reduce or eliminate withdrawal symptoms associated with opioid dependence. It is taken daily via sublingual tablets or films. It typically is given as a combination medication with naloxone to discourage misuse, because naloxone will trigger uncomfortable withdrawal symptoms if injected. Per U.S. federal regulations, a DEA waiver, obtained by an 8-hour online or in-person course, is required before prescribing buprenorphine. An adolescent-focused version of the waiver training course is found at *www.aap.org/mat*.
- **Naltrexone** is a synthetic opioid antagonist that blocks opioids from binding to their receptors and thereby prevents their euphoric and other effects. It is more commonly given initially as a daily tablet and then as a monthly depot injection. In theory, the repeated absence of the desired effects of the opioids diminishes the cravings.
- **Methadone** is a long-acting synthetic full opioid agonist medication that can prevent withdrawal symptoms and reduce craving in opioid-addicted individuals. This is most effective when used in combination with behavioral treatment and counseling.

Carney BL, Hadland SE, Bagley SM. Medication treatment of adolescent opioid use disorder in primary care. *Pediatr Rev.* 2018;39(1):43–45.

KEY POINTS: SUBSTANCE ABUSE

1. Adolescents should be screened with the CRAFFT tool for substance use and abuse at routine visits.
2. Brief counseling to address smoking initiation, cessation, and to prevent relapse can be effective in as little as 3 minutes.
3. Drug and alcohol use can have significant physical and mental health complications.
4. Opioid overdose can be identified by pinpoint pupils, unconsciousness, and respiratory depression. The antidote for opioid overdose is naloxone.

TEENAGE MALE DISORDERS

120. How common is gynecomastia in teenage boys?

Gynecomastia, enlargement or swelling of breast tissue, occurs in as many as **60% to 70%** of adolescent boys. In most, it spontaneously resolves in 1 to 2 years; 25% have persistence $\geq$2 years. It occurs most commonly during Tanner stages II and III, and it usually consists of subareolar enlargement (breast bud). It may be unilateral or bilateral. The breast bud may be tender, which indicates the recent rapid growth of tissue. Obese boys often have breast enlargement due to the deposition of adipose tissue, and differentiation from gynecomastia (true breast budding) is sometimes difficult.

Guss CE, Divasta AD. Adolescent gynecomastia. *Pediatr Endocrinol Rev.* 2017;14(4):371–377.
Bell DL, Breland DJ, Ott MA. Adolescent and young adult male health: a review. *Pediatrics.* 2013;132(3):535–546.

121. Why does gynecomastia occur so commonly in young teenage boys?

Early during puberty, the production of estrogen (a stimulator of ductal proliferation) increases relatively faster than does that of testosterone (an inhibitor of breast development). This slight imbalance causes the breast enlargement. In obese teenagers, the enzyme aromatase (found in higher concentrations in adipose tissue) converts testosterone to estrogen.

122. Which boys with gynecomastia warrant further evaluation?

- Prepubertal or postpubertal boys
- Pubertal-age boys with little or no virilization and small testes
- Boys with hepatomegaly or abdominal mass palpated
- Boys with CNS complaints

Evaluation may include testing for hypothalamic or pituitary disease (e.g., prolactinoma), feminizing tumors of the adrenal or testes, and genetic abnormalities (e.g., Klinefelter syndrome). Although breast cancer is extremely rare in men (0.2%), the rate increases to 3% to 6% in patients with Klinefelter syndrome. Benign cases of gynecomastia should be managed with reassurance. Plastic surgery is a last-resort option if the gynecomastia does not resolve and is causing significant distress.

Guss CE, Divasta AD. Adolescent gynecomastia. *Pediatr Endocrinol Rev.* 2017;14(4):371–377.
Nuzzi LC, Firriolo JM, Pike CM, et al. The effect of surgical treatment for gynecomastia on quality of life in adolescents. *J Adolesc Health.* 2018;63(6):759–765.

123. What are the clinical manifestations of testicular torsion?

Testicular torsion in adolescents usually presents with acute-onset hemiscrotal pain that may radiate to the groin and lower abdomen. Nausea and vomiting are also common. The testis is acutely tender and may be elevated, indicating a twisted and foreshortened spermatic cord. The cremasteric reflex (the testicle retracts after light stroking of the ipsilateral thigh) is typically absent. In the setting of acute torsion, many patients report previous episodes of severe acute scrotal pain.

124. When is testicular torsion likely to occur?

Testicular torsion has a **peak incidence at ages 15 to 16**, with two-thirds of cases occurring between ages 12 and 18. This is felt to be due to the increasing weight of the testicle during puberty. The most common underlying factor leading to testicular torsion is a congenital malformation called the *"bell-clapper" deformity*. The bell-clapper deformity refers to an abnormal fixation of the tunica vaginalis to the testicle, resulting in a horizontal lie of the testis and increased mobility of the testis. Of note, the other peak of testicular torsion occurs in the neonatal period.

Sharp VJ, Kieran K, Arlen AM. Testicular torsion: diagnosis, evaluation, and management. *Am Fam Physician.* 2013;88(12): 835–840.

125. How is testicular torsion diagnosed?

Because salvage of the testis depends on the timely restoration of blood flow, imaging studies should not delay surgical exploration if symptoms and physical examination findings strongly suggest torsion. Ultrasound with color Doppler is sensitive and specific, fast to perform, and often readily available, making it the modality of choice for imaging if the presentation warrants further investigation. Low or absent blood flow to the testis seen on Doppler is suggestive of torsion.

126. How is testicular torsion treated?

Manual detorsion of the spermatic cord may be attempted if prompt surgical intervention is not available. However, surgical exploration is still required for fixation to prevent recurrence. Most surgeons believe that the contralateral testicle should also undergo fixation to reduce the risk for asynchronous torsion, because inadequate fixation is usually a bilateral defect.

Bowlin PR, Gatti JM, Murphy JP. Pediatric testicular torsion. *Surg Clin North Am.* 2017;97(1):161–172.

127. If complete testicular torsion has occurred, how long is it before irreversible changes develop?

Irreversible changes develop in **4 to 8 hours**. Reported testicular salvage rates are 90% to 100% if surgical exploration occurs within 6 hours of symptoms, 50% if symptoms are present for more than 12 hours, and less than 10% if symptom duration is 24 hours or longer.

128. What are some other causes of acute scrotal pain?

- **Epididymitis**: An inflammatory process that is usually slower in onset, and pain is initially localized to the epididymis, but as inflammation spreads, the entire testis may become painful. This may be associated with nausea, fever, abdominal or flank pain, dysuria, and/or urethral discharge, and pain does not usually radiate to the groin. Epididymitis is often caused by chlamydia or gonorrhea, and a history of STIs is suggestive.
- **Orchitis**: Usually slower in onset, often has systemic symptoms (nausea, vomiting, fever, chills), and is a result of diffuse viral infection. In patients with mumps, orchitis occurs about 4 to 8 days after parotitis, bilateral involvement is more common, and is usually seen in 7- to 12-year-olds.
- **Torsion of appendix testis**: Sudden onset of pain localized to the superior aspect of the testicle (occasionally with bluish discoloration, the so-called *blue-dot sign*). Nausea and vomiting are uncommon. This is usually seen in prepubertal boys, and the cremasteric reflex is usually present.
- **Incarcerated hernia:** Acute-onset pain not localized to the hemiscrotum. There is usually a palpable inguinal mass. The testes are not painful, and there may be symptoms and signs of bowel obstruction (vomiting, abdominal distention, guarding, rebound tenderness).

129. Is a routine testicular examination currently recommended?

The U.S. Preventive Services Task Force (USPSTF) recommends against clinician examination or patient self-examination to screen for testicular cancer among asymptomatic adolescent or adult men. One rationale is that there is lack of evidence that screening would significantly decrease the cancer mortality rate, given the low incidence and high cure rate of testicular cancer. No studies have examined the sensitivity or specificity of self-examination or clinical examination for testicular cancer. The USPSTF cites an increased rate of false positives (and associated anxiety and harm from diagnostic procedures) as a potential harm associated with screening. However, other organizations dispute this negative recommendation, citing the benefits of testicular self-examination beyond cancer detection, such as detection of varicoceles.

Rovito MJ, Leone ME, Cavayero CT. "Off-label" usage of testicular self-examination (TSE): benefits beyond cancer detection. *Am J Mens Health.* 2018;12(3):505–513.

U.S. Preventive Services Task Force Screening for Testicular Cancer. U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* 2011;154(7):483–486.

130. What is the significance of a varicocele in a teenager?

A *varicocele* is an enlargement of either the pampiniform or cremasteric venous plexus of the spermatic cord, which results in a boggy enlargement ("bag of worms)" of the upper scrotum. These are rare before puberty. About 15% of boys between the ages of 12 and 18 have a varicocele, and about 10% of those are symptomatic (pain, discomfort). Longitudinal studies of adolescents show that large varicoceles may interfere with normal testicular growth and result in decreased spermatogenesis.

131. Which varicoceles warrant surgical intervention?

It is controversial whether surgery can prevent the potential fertility consequences of varicoceles. The three primary indications for surgical intervention are:

- Varicocele with testicular atrophy on the ipsilateral side (>20% volume difference)
- Testicular pain
- Altered semen analysis

Pastuszek AW, Kumar V, Shah A, Roth DR. Diagnostic and management approaches to pediatric and adolescent varicocele: a survey of pediatric urologists. *Urology.* 2014;84(2):450–455.

132. On which side do varicoceles more commonly occur?

The left side. The left spermatic vein drains into the left renal vein at a right angle, and the right spermatic vein drains into the inferior vena cava at an obtuse angle. The hemodynamics favor higher left-sided pressures, which predispose patients to left-sided varicoceles. Unilateral left-sided varicoceles are the most common type, occurring in 90% of patients; the remainder are bilateral. A unilateral right-sided lesion is rare, and many experts consider its presence a reason to search for other causes of venous obstruction, such as a renal or retroperitoneal tumor.

133. What is the difference between phimosis and paraphimosis?

- *Phimosis* is constriction of the prepuce orifice that prevents the foreskin from being withdrawn to reveal the glans penis. It can be secondary to minor inflammation from normal erections and from poor hygiene. Treatment is initially conservative with topical steroid creams, but circumcision may be considered in resistant cases.
- *Paraphimosis*, on the other hand, is retraction of the foreskin behind the glans with inability to reposition it back. This is a medical emergency and requires surgical intervention. If untreated, paraphimosis can lead to penile ischemia.

134. What are pearly penile papules, and should a teen worry about them?

Pearly penile papules *(hirsuties coronae glandis)* are 1- to 3-mm papules of the same size and shape distributed symmetrically along the corona of the glans penis. These papules are an anatomic variation and not infectious. They occur in about 15% to 20% of adolescent boys. There is a higher incidence in uncircumcised males. No treatment is indicated. Providers should reassure the teen that this is a normal finding.

Leung AK, Barankin B. Pearly penile papules. *J Pediatr.* 2014;165(2):409.

KEY POINTS: TEENAGE MALE DISORDERS

1. Gynecomastia is very common in adolescent males, but additional evaluation is warranted if present in prepubertal or postpubertal boys, those with little or no virilization and small testes, those with hepatomegaly, or boys with CNS complaints.
2. Testicular torsion is a surgical emergency, as irreversible changes occur within 4 to 8 hours. Testicular salvage is almost universal if surgical exploration occurs within 6 hours of symptoms.
3. Left-sided varicoceles are more common than right-sided and only warrant a workup if symptomatic or if associated with testicular atrophy. Right-sided varicoceles deserve a workup.

TEENAGE PREGNANCY AND CONTRACEPTION

135. What is the trend for teen pregnancy rates in the United States?

Teenage pregnancy rates have continued to fall steadily in the last two decades, except for a brief increase between 2006 and 2007. Although pregnancy rates continue to decline, U.S. teen pregnancy rates are among the highest in the developed world. Teen pregnancy rates for black and Hispanic teens remain consistently at least twice that of white teenagers. About 80% of teen pregnancies are unintended, and about one-third end in abortion. The teenage abortion rate in 2015 was the lowest since abortion was legalized (in 1973). About half of U.S. teen pregnancies progress to delivery.

CDC. www.cdc.gov/nchs/data/databriefs/db318.pdf. Accessed June 27, 2019.

136. How likely is a teen mother to become pregnant and give birth to another child?

- According to the CDC, nearly one in five births to adolescent mothers ages 15–19 is a repeat birth.
- Factors associated with a repeat teen pregnancy include young age at first conception, intended first pregnancy, lack of contraceptive use, poor outcome of first birth, low school achievement, regular use of alcohol or drugs, poor family involvement, low level of parental education, and being the product of a teen pregnancy.

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https://www.cdc.gov/vitalsigns/teenpregnancy/index.html; accessed January 15, 2020.

Martin JA, Hamilton BE, Osterman MJ, Driscoll, AK, Drake P. *Births: final data for 2016. Hyattsville*, MD: National Center for Health Statistics. From https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_01.pdf. Accessed on April 17, 2018.

137. What are the risks for infants of teenage mothers?

Babies born to young teenage mothers are more likely to be preterm, have low birth weight, or be small for gestational age. In addition, infant mortality is greater for the infants of teenage mothers. It is unclear whether these risks are due to physiologic effects of adolescent pregnancy or to sociodemographic factors associated with teenage pregnancy (e.g., poverty, inadequate prenatal care).

Ganchimeg T, Ota E, Morisaki N, et al. Pregnancy and childbirth outcomes among adolescent mothers: a World Health Organization multicountry study. *BJOG.* 2014;121(Suppl 1):40–48.

138. How soon after conception will a urine pregnancy test become positive?

Human chorionic gonadotropin (hCG) is a glycoprotein that is produced by trophoblastic tissue. Urine pregnancy tests can detect pregnancy by measuring total hCG, hyperglycosylated hCG, or the free β subunit of hCG. Urine levels of 25 mIU/mL hCG are detectable by the most sensitive tests **by about 7 days after fertilization**. Although many home pregnancy tests can detect these low levels, some are less sensitive and can only accurately diagnose pregnancy by about 3 days after the missed menstrual period.

Cole LA. The hCG assay or pregnancy test. *Clin Chem Lab Med.* 2012;50(4):617–630.

139. In what setting should ectopic pregnancy be suspected?

Amenorrhea with unilateral abdominal or pelvic pain, **irregular vaginal bleeding**, and **abdominal pain with positive pregnancy test** are indicative of ectopic pregnancy until proven otherwise. A teenager with a ruptured ectopic pregnancy can present with features of shock (hypotension, tachycardia) and rebound tenderness. Sequential hCG levels can help in differentiating an ectopic from an intrauterine pregnancy. For a viable intrauterine pregnancy, the doubling time of hCG levels is about 48 hours; in ectopic pregnancy, there is usually a significant lag. Other causes of lag include missed abortion and spontaneous abortion. Ultrasound is the first-line imaging modality for diagnosis. Laparoscopy may be necessary if the diagnosis remains unclear.

Barnhart KT. Ectopic pregnancy. *N Engl J Med.* 2009;361(4):379–387.

140. Which contraceptive methods are appropriate for adolescents?

All available reversible methods of contraception are appropriate for use in adolescents, barring specific medical contraindications. These include long-acting reversible contraception (LARC), such as IUDs and progestin implants, progestin-only injectable contraception, combined hormonal contraception (birth control pills), and barrier methods. The AAP recommends that pediatricians should counsel on the use of contraception based on the effectiveness and convenience of each method.

Raidoo S, Kaneshiro B. Contraception counseling for adolescents. *Curr Opin Obstet Gynecol.* 2017;29(5):310–315.

Ott MA, Sucato GS; Committee on Adolescence. Contraception for adolescents. *Pediatrics*. 2014;134(4):e1257–e1281.

141. Are IUDs safe for use in teenagers?

LARC methods available include IUDs. In the past, myths about the safety of IUD use in adolescents and in nulliparous women discouraged providers from taking advantage of these highly effective methods. However, it is now known that methodologic flaws in prior studies exaggerated the risks in the adolescent population and that these methods are safe for use in teens. IUDs do not significantly increase the risk for pelvic infections, outside of the 3-week window after insertion, and do not cause infertility.

Itriyeva K. Use of long-acting reversible contraception (LARC) and the Depo-Provera shot in adolescents. *Curr Probl Pediatr Adolesc Health Care.* 2018;48(12)321–332.

142. What are significant side effects of the progestin-only injectable contraceptive method?

The injectable progestin-only contraception available in the United States (Depo-Provera) is a common type of hormonal contraception used by adolescents. It is dosed every 3 months. Weight gain and intermenstrual bleeding are side effects associated with this method. Although bone mineral loss may be associated with this method, users do not appear to have an increased risk for fractures.

Itriyeva K. Use of long-acting reversible contraception (LARC) and the Depo-Provera shot in adolescents. *Curr Probl Pediatr Adolesc Health Care.* 2018;48(12)321–332.

143. What are the different forms of combined estrogen and progesterone hormonal contraception?

Combined estrogen and progestin contraception methods include the combined oral contraceptive pill (COC), patch, and vaginal ring. These methods have the same mechanism of action but vary in their delivery systems and dosing intervals, from daily dosing (COCs) to monthly dosing (vaginal ring). Despite excellent efficacy with perfect use, failure rates for typical use are about 9 pregnancies per 100 women and may be higher for adolescents because missed doses are common.

Raidoo S, Kaneshiro B. Contraception counseling for adolescents. *Curr Opin Obstet Gynecol.* 2017;29(5):310–315.
Ott MA, Sucato GS. Contraception for adolescents. *Pediatrics.* 2014;134(4):e1257–e1281.

144. How effective are male and female condoms as contraceptive methods?

Condoms have relatively high typical-use failure rates for pregnancy prevention (18% for male condoms and 21% for female condoms). Therefore, dual contraceptive method use (i.e., hormonal contraception together with a barrier method) should be encouraged. However, condoms are the only contraceptive methods that also provide protection against STIs.

Ott MA, Sucato GS. Contraception for adolescents. *Pediatrics.* 2014;134(4):e1257–e1281.

145. What are contraindications to the use of estrogen-containing contraceptive methods?

Estrogen is the hormonal component of contraception with the greatest number of medical contraindications. Absolute contraindications that should preclude an estrogen-containing method include:

- Migraine headaches with aura
- Personal history of deep venous thrombosis
- Known thromboembolic disorder, including lupus with antiphospholipid antibody syndrome and familial factor V Leiden deficiency
- Untreated hypertension (>160/100)
- Major surgery with prolonged immobilization
- Complicated valvular heart disease
- Coronary artery disease
- Stroke
- Acute or chronic liver disease with abnormal liver function
- Breast, endometrial, or other estrogen-sensitive cancer

Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR.* 2016;65(No. RR-3):1–104.

146. Is a pelvic examination mandatory before starting a patient on contraception?

No. Numerous professional organizations, including the American College of Obstetricians and Gynecologists, concur that a pelvic examination is not required for safe initiation of contraception. A large percentage of teenagers will delay seeking contraceptive care if they believe a pelvic examination is required. Routine pelvic examination and Pap smears should begin at age 21, regardless of sexual activity or contraceptive use.

ACOG Committee Opinion No. 615. Access to contraception. *Obstet Gynecol.* 2015;125:250–255.

147. What oral treatments are used for emergency postcoital contraception?

- **Levonorgestrel (Plan B and generics)** is a U.S. FDA-approved progestin-only method, now available in a one-pill formulation (1.5 mg of levonorgestrel) taken as soon as possible after intercourse. This method has been approved for over-the-counter sale (without a prescription) in the United States regardless of age. Progestin-only emergency contraception acts by inhibiting or delaying ovulation, disrupting follicular development, thickening cervical mucus to impede sperm penetration, and affecting the maturation of the corpus luteum. Levonorgestrel can reduce the risk for pregnancy by at least 75% when given within 72 hours of unprotected intercourse, and studies show that it maintains good efficacy when taken up to 120 hours later.
- **Ulipristal acetate (Ella)** is another FDA-approved emergency contraceptive method available by prescription only in the United States. This method maintains stable efficacy up to 5 days after intercourse.
- The **copper IUD** can also be used as emergency contraception when inserted within 5 days of unprotected intercourse and is the most effective method of emergency contraception.

Batur P, Kransdorf LN, Casey PM. Emergency contraception. *Mayo Clin Proc.* 2016;91(6):802–807.

KEY POINTS: TEENAGE PREGNANCY AND CONTRACEPTION

1. Teen pregnancy has been steadily declining over the past two decades; however, teens are at high risk for repeat pregnancy, and infants born to teenage mothers are at high risk for adverse health outcomes.
2. Pediatricians should counsel adolescents on contraception based on the efficacy and convenience of each method.
3. LARC, such as IUDs and implants, are safe and effective for most adolescents.
4. The three methods of emergency contraception available to adolescents that may be used within 5 days of unprotected sex include levonorgestrel (Plan B), ulipristal acetate (Ella), and the copper IUD.

TEENAGE SUICIDE

148. What are the three leading causes of mortality in adolescents in the United States?

1. **Unintentional injury** is the leading cause of death, accounting for 40% of total adolescent deaths, with the majority of injuries caused by car crashes. The fatal crash rate per mile driven for 16- to 17-year-olds is about three times greater than the rate for drivers 20 and older. Of those adolescents who drove a car on at least 1 day during the 30 days before the survey, approximately 40% had texted or e-mailed while driving.
2. **Suicide** is the second leading cause of death in adolescents aged 10 to 24 years, at nearly 18% of total deaths.
3. **Homicide** is the third leading cause of death among 10- to 24-year-olds and the leading cause for black males between 15 and 24 years old.

Heron M. Deaths: leading causes for 2016. *Natl Vital Stat Rep.* 2018;67(6):1–77.
Kann L, McManus T, Harris WA, et al. Youth risk behavior surveillance—United States, 2017. *MMWR.* 2018;67(8):1–114.

149. Why is depression screening for adolescents recommended by the AAP?

- Depression is very common among adolescents. Almost one-third of U.S. high school youth have reported feeling sad or hopeless for at least 2 weeks at a time within the previous year.
- Depression may present with a combination of the following symptoms: sad mood or irritability, anhedonia, fatigue, changes in appetite and/or sleep, inability to concentrate, agitation or psychomotor slowing, feelings of guilt or low self-worth, and having persistent thoughts of death or a desire to hurt oneself.
- Over two-thirds of youth with depression go untreated, as their depression is not recognized in primary care settings.

These are reasons why the AAP has advised screening for depression, using one of a variety of screening tools, at ages 11 through 21 at all well-visits.

Zuckerbot RA, Cheung A, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): part I. Practice preparation, identification, assessment, and initial management. *Pediatrics.* 2018;141(3):e20174081.

150. How common is suicidal ideation and suicide attempts in adolescents?

In 2017, 17% of high school students surveyed reported having seriously considered suicide, and 7.4% admitted to having made a suicide attempt in the past year. Of note, only about one-third of adolescents who attempt suicide come to medical attention.

Kann L, McManus T, Harris WA, et al. Youth risk behavior surveillance—United States, 2017. *MMWR.* 2018;67(8):1–114.

151. Who are more likely to attempt suicide, males or females?

Females have greater odds of both suicidal ideation and suicide attempt compared with males. However, males (particularly white males) are much more likely to succeed, due in large part to the choice of more lethal methods (especially firearms). In younger patients (10 to 14 years), suffocation (such as hanging) is the most common method used.

152. Which adolescents are at increased risk for suicide?

Adolescents who are most at risk are those with:

- A history of a preexisting psychiatric disorder, especially major depression, bipolar disorder, or conduct disorder
- A history of previous suicide attempts, especially those involving potentially lethal methods and those that occurred within the past 2 years
- Easy access to firearms (most common location for teenage suicide involving firearms is in the home)
- History of impulsive aggression or acute agitation
- Family history of suicide and depression
- Family discord
- Loss of a parent to death or divorce
- Sexual minority (LGBTQ) adolescents, especially if unsupportive family or hostile school environment
- Substance abuse (both illicit drugs and alcohol)
- A history of physical and/or sexual abuse

Shain B. Suicide and suicide attempts in adolescents. *Pediatrics.* 2016;138(1):e20161420.

153. A 15-year-old girl with a history of depression presents with linear superficial lacerations over her left forearm. What is the likely diagnosis?

Deliberate self-harm (also known as **nonsuicidal self-injury or "cutting"**) in U.S. youth is relatively common and has been reported in up to 10% of high school–aged males and 25% of high school–aged females. Nonsuicidal self-injury in youth is associated with depression, suicidal ideation and attempts, sexual minority status, being the victim of cyberbullying, and substance use.

Monto MA, McRee N, Deryck FS. Nonsuicidal self-injury among a representative sample of US adolescents, 2015. *Am J Public Health.* 2018;108(8):1042–1048.

CHAPTER 2

BEHAVIOR AND DEVELOPMENT

Mark F. Ditmar, MD

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

1. What are the characteristics of attention-deficit/hyperactivity disorder (ADHD)?

ADHD is a chronic neurodevelopmental and behavioral disorder, considered to have neurobiologic origins, that is diagnosed on the basis of the number, severity, and duration of three clusters of behavioral problems: *inattention*, *hyperactivity*, and *impulsivity*. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), symptoms of inattention, hyperactivity, and impulsivity must have lasted for more than 6 months and be inconsistent with the child's developmental level. These symptoms have to involve more than one setting and result in significant functional impairment at home, school, or in social settings. Some symptoms must have begun before the age of 13 years.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013:59–61.

2. How common is ADHD?

Community prevalence studies indicate that 4% to 12% of school-age children are affected by ADHD. It is the **most common neurodevelopmental disorder** in the United States.

3. Are boys or girls more likely to be diagnosed with ADHD?

Males are three to four times more frequently diagnosed with ADHD. Their symptoms tend to be more disruptive, particularly with hyperactivity, whereas girls present more commonly with problems of attention.

4. What is the cause of ADHD?

The pathogenesis remains unknown. Because of differences noted in structural and functional brain imaging between children with and without ADHD, as well as the positive therapeutic response to medications with noradrenergic activity, a primary role appears to be an imbalance of metabolism of neurotransmitters, particularly catecholamines, in the cerebral cortex.

Thapar A, Cooper M, Jefferies R, Stergiakouli E. What causes attention deficit hyperactivity disorder? *Arch Dis Child.* 2012;97(3):260–265.

5. Is there a genetic predisposition to ADHD?

ADHD has a **high rate of heritability**. In studies of identical twins raised apart, if one twin has ADHD, the other has up to a 75% likelihood of being diagnosed with ADHD. In nonidentical twin studies, the concordance rate is as high as 33%. Studies of siblings of patients with ADHD indicate a 20% to 30% likelihood. About 25% of children with ADHD have at least one parent with symptoms or a diagnosis of ADHD. Genome-wide linkage and fine mapping studies support the linkage between ADHD and various chromosomal bands and candidate genes. Genes that regulate dopaminergic pathways are suspected to be involved in ADHD's pathogenesis. However, gene variants suspected in ADHD are only weakly predictive and currently have only limited clinical value.

Thapar A. Discoveries on the genetics of ADHD in the 21st century: new findings and their implications. *Am J Psychiatry.* 2018;175(10):943–950.

Dark C, Homman-Ludiye J, Bryson-Richardson RJ. The role of ADHD genes in neurodevelopment. *Dev Biol.* 2018;438(2):69–83.

6. Is there a definitive diagnostic test for ADHD?

No. Diagnosis requires evidence of characteristic symptoms occurring in high frequency over an extended period. This information, which is ideally obtained from at least two settings or sources (e.g., school and home), can be garnered from observation, narrative histories, and the use of various standardized rating scales. The use of validated ADHD questionnaires is recommended by the American Academy of Pediatrics (AAP), but these rating scales are underutilized in diagnostic evaluation (only about 50% of the time) and in therapeutic monitoring after treatment (10% or less of the time).

Barbaresi WJ. Improving care for children with ADHD: the information is just a rating scale away. *Pediatrics.* 2016;137(3):e20154450.

American Academy of Pediatrics. ADHD clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics.* 2011;128(5):1007–1022.

7. How should ADHD be treated?

A multimodal approach is recommended, which may include psychotropic medication, behavioral therapies, family education and counseling, and educational interventions.

Feldman HM, Reiff MI. Attention deficit-hyperactivity disorder in children and adolescents. *N Engl J Med.* 2014;370(9):838–846.

8. What are the best medications for treating ADHD?

Stimulant medications (methylphenidate, mixed amphetamine salts, and dextroamphetamine) are typically first-line treatments. Randomized, controlled trials support their benefits, usually by demonstrating an improvement of core ADHD symptoms in 70% to 80% of children. Of the 20% to 30% of nonresponders to one medication, about one-half will respond to the other stimulant. Other medications used to treat ADHD include atomoxetine (a norepinephrine-reuptake inhibitor), central α-adrenergic agonists (e.g., clonidine), tricyclic antidepressants, and atypical antidepressants (e.g., bupropion). There is concern about the possible overuse of stimulants in children of all ages.

Southammakosane C, Schmitz K. Pediatric psychopharmacology for treatment of ADHD, depression and anxiety. *Pediatrics.* 2015;136(2):351–359.

9. Is a positive response to stimulant medication diagnostic of ADHD?

A positive response is not diagnostic because (1) children without symptoms of ADHD given stimulants demonstrate positive responses in sustained and focused attention and (2) observer bias (i.e., parent or teacher) can be considerable. Thus many experts recommend a placebo-controlled trial when stimulant medication is used.

10. Is an electrocardiogram (ECG) required before beginning patients on stimulant medication for ADHD?

This is controversial. Case reports of sudden death among pediatric patients treated with ADHD medications prompted the U.S. Food and Drug Administration (FDA) in 2005 to 2006 to issue warnings on stimulant medication use in ADHD patients. The American Heart Association listed the indication for an ECG in this setting as class II, indicating uncertainty as to its need or lack of need. Large studies subsequently did not demonstrate an increased risk compared with the background rate of sudden death. Many pediatric cardiologists do not recommend an ECG because the ECG as a screening test has low positive and negative predictive values in this low-risk population.

Shahani SA, Evans WN, Mayman GA, et al. Attention deficit hyperactivity disorder screening electrocardiograms: a community-based perspective. *Pediatr Cardiol.* 2014;35(3):485–489.

Martinez-Raga J, Knecht C, Szerman N, et al. Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. *CNS Drugs.* 2013;27(1):15–30.

11. How young is “too young” to diagnose ADHD and prescribe stimulant medications?

The AAP recommends an initial evaluation for ADHD for any child **as young as age 4 years** with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity. Behavior therapy is advised as the first line of treatment, but methylphenidate may be prescribed if behavior therapy results in no significant improvement and moderate to severe disturbance is occurring in the child’s function. Treatment of preschool children, however, is controversial.

Tandon M, Pergjika A. Attention deficit hyperactivity disorder in preschool-age children. *Child Adolesc Psychiatr Clin N Am.* 2017;26(3):523–538.

American Academy of Pediatrics. ADHD clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics.* 2011;128(5):1007–1022.

12. What are the risks for adolescents with ADHD?

Risks for adolescents involve **increased high-risk behaviors**, including higher rates of sexually transmitted infections and pregnancies, and **increased school problems**, including higher rates of grade failure, dropping out, and expulsion. Untreated ADHD has also been found to be a significant risk factor for substance abuse and for automobile accidents.

Curry AE, Yerys BE, Metzger, KB, et al. Traffic crashes, violations and suspensions among young drivers with ADHD. *Pediatrics.* 2019;143(6):e20182305.

KEY POINTS: THE “I”-SSENTIALS OF ADHD

Inattention
Increased activity
Impulsiveness
Impairment in multiple settings
Inappropriate (for developmental stage)
Incessant (persists for >6 months)

13. Does sugar or food additives make children hyperactive?

Although it would be gratifying if complex behavioral problems could be attributable solely or in large measure to dietary causes, the majority of controlled studies have failed to demonstrate any significant exacerbations of symptoms from the intake of sucrose or aspartame.

Millichap JG, Yee MM. The diet factor in attention-deficit/hyperactivity disorder. *Pediatrics.* 2012;129(2):330–337.

14. Are nonpharmacologic therapies beneficial for ADHD?

These can range from highly structured behavioral interventions to complementary medicines. Many are tried by frustrated parents (often unbeknownst to the primary care provider), such as neurofeedback, megadose vitamin therapy, herbals, and dietary modifications. However, randomized controlled trials are few and, when done, typically demonstrate no benefit.

Goode AP, Coeytaux RR, Maslow, GR, et al. Nonpharmacologic treatments for attention-deficit/hyperactivity disorder: a systematic review. *Pediatrics.* 2018;141(6):e20180094.

15. Do children with ADHD become teenagers and adults with ADHD?

Ongoing observations of children initially diagnosed with ADHD note that 70% to 80% will continue to have symptoms present during adolescence and up to 60% will show symptoms as adults. Of the features of ADHD, hyperactivity is the symptom most likely to be outgrown. Inattention, distractibility, and failure to finish things are more likely to persist. Adolescents and adults also have continued problems with anxiety and depression, as well as with tobacco and substance abuse. Motor vehicle infractions, employment difficulties, and intimate relationships have also been described as problematic for adults. Children and adolescents with severe symptoms, mental health problems in parents, and childhood comorbidities (such as conduct disorder or depression) are at the highest risk for severe problems as adults.

Hechtman L, Swanson JM, Sibley MH, et al. Functional adult outcomes 16 years after childhood diagnosis of attention-deficit/hyperactivity disorder: MTA results. *J Am Acad Child Adolesc Psychiatry.* 2016;55(11):945–952.e2.

Roy A, Hechtman L, Arnold LE, et al. Childhood factors affecting persistence and desistence of attention-deficit/hyperactivity disorder symptoms in adulthood: results from the MTA. *J Am Acad Child Adolesc Psychiatry.* 2016;55(11):937–944.e4.

AUTISM

16. What is the DSM-5?

The DSM is the ***Diagnostic and Statistical Manual of Mental Disorders***, which is published by the American Psychiatric Association on a periodic basis to diagnose and classify mental and behavioral disorders. Criteria for diagnoses are commonly changed to improve diagnostic accuracy based on new research and ongoing psychiatric practice, but classifications can be controversial. The latest version, DSM-5, was released in May 2013. It replaced the DSM-4, which had been introduced in 1994 and had undergone a number of revisions.

Baker JP. Autism at 70—redrawing the boundaries. *N Engl J Med.* 2013;369(12):1089–1091.

17. How did classifications change for disorders of autism in the DSM-5?

Previously, autism spectrum disorders (ASDs) were classified into groups including Asperger syndrome, pervasive developmental disorder, not otherwise specified (PDD-NOS), childhood disintegrative disorder (with developmental deterioration after 24 months of age), and autistic disorder. The DSM-5 eliminated these separate subcategories and folded all individual groups into the broader term of *ASD* with two essential features (see question 19). Clinicians rate the severity of autistic features to classify patients with severity dependent on the extent of support required to compensate for problems with social communication/interaction and repetitive/restrictive behaviors.

American Psychiatric Association. *Diagnosis and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013:50.

Autism Society of America. www.autism-society.org. Accessed January 15, 2020.

Autism Speaks. www.autismspeaks.org. Accessed January 15, 2020.

18. How is the diagnosis of autism established?

Behavioral, historical, and parental reports are assessed, commonly by a multidisciplinary team, through the use of a number of possible diagnostic tools, including the Autism Behavior Checklist (ABC) and the Autism Diagnostic Observation Schedule (ADOS). These tools can include questionnaires, checklists, and direct-observation assessments of a child's social interaction, communication, and imaginative play.

Randall M, Egberts KJ, Samtani A, et al. Diagnostic tests for autism spectrum disorder (ASD) in preschool children. *Cochrane Database Syst Rev.* 2018;7:CD009044.

Falkmer T, Anderson K, Falkmer M, et al. Diag[illegible]tic procedures in autism spectrum disorders: a systematic literature review. *Eur Child Adolesc Psychiatry.* 2013;22(6):329–340.

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19. What are the two essential features of autism?

- ***Impaired social interaction and social communication*** (e.g., extreme aloneness, failure to make eye contact, deficit in nonverbal communicative behaviors for social interaction, deficits in maintaining and understanding relationships)
- ***Restricted and repetitive patterns of behavior*** (e.g., insistence on sameness or inflexible adherence to routines, stereotyped or repetitive responses to objects, narrow range of interests, hyperreactivity to sensory input, unusual interest in sensory aspects of the environment)

KEY POINTS: TWO ESSENTIAL FEATURES OF AUTISM

1. Impaired social interaction and social communication
2. Restricted and repetitive patterns of behavior

20. Which behaviors of children should arouse suspicion of possible autism?

- Avoidance of eye contact during infancy (“gaze aversion”)
- Relating to only part of a person’s body (e.g., the lap) rather than to the whole person
- Failure to acquire speech or speech acquisition in an unusual manner (e.g., echolalia [repeating another person’s speech])
- Failure to respond to name when called
- Spending long periods in repetitive activities and fascination with movement (e.g., spinning records, dripping water)
- Failure to look in the same direction when directed by an adult (“gaze monitoring”)
- Absence of pointing to show or request something (“protodeclarative pointing”)
- Excessively lining up toys or other objects
- Limited pretend or symbolic play

Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders, *Pediatrics.* 2007;120(5):1183–1215.

21. When should screening be done for autism?

The AAP recommends that all children receive autism-specific screening at 18 and 24 months and whenever there is a concern for autism. Younger siblings of patients with autism have a 10- to 20-fold increased risk. Problems with preverbal gestural language and deficits in social skills are present in most children by 18 months of age. Early recognition of autism can lead to earlier intervention, which can improve outcomes markedly. A 20-question M-CHAT-R/F (Modified Checklist for Autism in Toddlers, Revised with Follow-up) is the most commonly used screening questionnaire for children ages 18 to 30 months, although accuracy may be only low to moderate in younger or low-risk children. Other screening tools are available for children younger and older than this age range.

Yuen T, Penner M, Carter MT, et al. Assessing the accuracy of the Modified Checklist for Autism in Toddlers: a systematic review and meta-analysis. *Dev Med Child Neurol.* 2018;60(11):1093–1100.

Robins DL, Casagrande K, Barton M, et al. Validation of the modified checklist for autism in toddlers, revised with follow-up (M-CHAT-R/F). *Pediatrics.* 2014;133(1):37–45.

22. What studies should be considered in the evaluation of a child with suspected autism?

- **Hearing screening**
- **Metabolic screening:** Urine for organic acids, serum for lactate, amino acids, ammonia, and very long-chain fatty acids (if there is developmental regression, intellectual disability, dysmorphic features, hypotonia, vomiting or dehydration, feeding intolerance, early-onset seizures, or episodic vomiting)
- **Karyotype, chromosomal microarray analysis, other genetic testing** (if there are dysmorphic features or intellectual disability; more than two dozen genetic syndromes are associated with autism)
- **DNA fragile X analysis** (if there is intellectual disability or phenotype of long, thin face and prominent ears)
- **Electroencephalogram** (especially if history of seizures, staring spells, or regression of milestones)
- **Neuroimaging with magnetic resonance imaging** (MRI) (especially if abnormal head shape or circumference, focal neurologic abnormalities, or seizures)
- **Lead level** (if history of pica)

Pickler L, Elias E. Genetic evaluation of the child with an autism spectrum disorder. *Pediatr Ann.* 2009;38(1):26–29.

23. What accounts for the apparent increase in autism in the United States?

Centers for Disease Control and Prevention (CDC) data indicated a 2014 prevalence rate of ASDs of 1 in 59 (1 in 37 boys, 1 in 151 girls) for children aged 8 years, which was a 13% increase from 2010 estimates of 1 in 68. In 2000, the CDC estimate was a prevalence rate of 1 in 150. Although some experts believe the condition per se is truly increasing in prevalence, other reasons may include diagnostic substitution (which assumes children were previously characterized as developmentally delayed rather than having ASD), broadening of the definition of ASD, and better screening and ascertainment. The largest increase in diagnosed cases has occurred among higher-functioning patients with less severe disease and in black and Hispanic populations.

CDC. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR.* 2018;67(6):1–23.
Harrington JW, Allen K. The clinician's guide to autism. *Pediatr Rev.* 2014;35(2):62–77.

24. Do vaccines cause autism?

Many claims have been made regarding possible environmental triggers for autism, including vaccines, particularly measles-mumps-rubella (MMR), and vaccine components, primarily thimerosal (a mercury-containing compound used as a preservative in some vaccines). The Institute of Medicine and numerous studies have found no links between the use of thimerosal or MMR vaccine as a cause of autism.

Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine.* 2014;32(29):3623–3629.
IOM (Institute of Medicine). *Adverse Effects of Vaccines: Evidence of Causality.* Washington, DC: The National Academies Press; 2012:145–153.

25. Does early intervention and/or therapy improve the outcome in children with autism?

In general, earlier diagnosis and involvement of therapies for children with autism do appear to improve outcomes, such as a decreased need for special education in later years and an increase in the chance for independence as an adult. Certain subsets of children with autism, such as those with no coexisting cognitive deficits, will fare better. Additionally, earlier recognition and intervention may assist families in understanding and coping with potentially challenging medical comorbidities and social and behavioral issues.

Zwaigenbaum L, Bryson S, Lord C, et al. Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants, *Pediatrics.* 2009;123(5):1383–1391.

BEHAVIOR PROBLEMS

26. What are the most common types of behavior problems in children?

- **Problems of daily routine** (e.g., food refusal, sleep abnormalities, toilet difficulties)
- **Aggressive-resistant behavior** (e.g., temper tantrums, aggressiveness with peers)
- **Overdependent-withdrawing behavior** (e.g., separation upset, fears, shyness)
- **Hyperactivity**
- **Undesirable habits** (e.g., thumb-sucking, head banging, nail biting, playing with genitals)
- **School problems**

Chamberlin RW. Prevention of behavioral problems in young children. *Pediatr Clin North Am.* 1982;29(2):239–247.

27. How much do babies normally cry each day?

In Brazelton's oft-quoted 1962 study of 80 infants, it was found that at 2 weeks of age, the average crying time was nearly 2 hours per day. This increased to nearly 3 hours per day at 6 weeks and then declined to about 1 hour per day at 12 weeks.

Brazelton TB. Crying in infancy. *Pediatrics.* 1962;29:579–588.

28. What is infantile colic?

Colic is excessive crying or fussiness, which occurs in 5% to 20% of infants depending on the criteria used. For study purposes, it is defined as paroxysms of crying in an otherwise healthy infant for >3 hours per day on >3 days per week for >3 weeks. The typical clinical picture is that of an otherwise healthy and well-fed baby (usually between the ages of 2 weeks and 3 months) who cries intensely and inconsolably for several hours at a time, usually during the late afternoon or evening. Often the infant appears to be in pain and has a slightly distended abdomen, with the legs drawn up; occasional temporary relief occurs if gas is passed.

The symptoms nearly always resolve by the time the infant is 3 to 4 months old, but the problem can have repercussions, including early discontinuation of breastfeeding, multiple formula changes, heightened maternal anxiety and distress, diminished maternal–infant interaction, and increased risk for child abuse.

29. What causes colic?

No precise cause has been identified, and the etiology is likely multifactorial. Theories have involved gastrointestinal dysfunction (e.g., intolerance or allergy to cow milk or soy protein, gastroesophageal reflux, lactose intolerance, immaturity of the gastrointestinal tract), neurologic problems (immaturity of the central nervous system [CNS], neurotransmitter imbalance), hormonal processes (e.g., increased serotonin), difficult infant temperament, and interaction problems between the infant and the caregiver (e.g., misinterpreted infant cues, transfer of parental anxiety).

30. Are there any treatments that are useful for colic?

As is the case for most self-resolving conditions without a known cause, **counseling** is the most effective treatment. However, multiple interventions with minimal effectiveness are often tried, and these can include elimination of cow milk from the breastfeeding mother's diet, formula changes (to soy or to protein hydrolysates), or a trial of herbal tea or simethicone to decrease intestinal gas. Probiotics have been studied as possible remedies, but clinical results are mixed. Medications such as antispasmodics are not recommended because of the risk for side effects. Other sensory modifiers (e.g., car rides, massage, swaddling) are also attempted to provide some course of action until the expected 3- to 4-month resolution.

Dryl R, Szajewska H. Probiotics for management of infantile colic: a systematic review of randomized controlled trials. *Arch Med Sci.* 2018;14(5):1137–1143.

31. What evaluations should be done for the excessively crying infant?

The infant with acute excessive crying (interpreted by caretakers as differing in quality and persisting beyond a reasonable time, generally 1 to 2 hours, without adequate explanation) can be a taxing problem for pediatricians and emergency room physicians. The differential diagnosis is broad, but infantile colic remains the most common diagnosis (and a diagnosis of exclusion). History and physical examination make the diagnosis in most infants. However, other tests to consider include stool for occult blood (possible intussusception), fluorescein testing of both eyes (possible corneal abrasion), urinalysis and urine culture (possible urinary tract infection), pulse oximetry (hypoxia from cardiac causes may manifest as increased irritability), and electrolytes and blood glucose (possible endocrine or metabolic disturbance).

Akhnikh S, Engelberts AC, van Sleuwen BE, et al. The excessively crying infant: etiology and treatment. *Pediatr Ann.* 2014;43(4):e69–e75.
Ditmar MF. Crying. In Schwartz MW, ed. *The 5-Minute Pediatric Consult.* 6th ed. Philadelphia, PA: Wolters Kluwer; 2012:236–237.

32. How should children be punished?

The goal of punishment should be to teach children that a specific behavior was wrong and to discourage the behavior in the future. To meet this goal, punishment should be consistent and relatively brief. It should be carried out in a calm manner as soon as possible after the infraction. Time-out from ongoing activity and removal of privileges are two punishment techniques that can be used. The use of corporal punishment is controversial. Although spanking and other physical forms of punishment are widely practiced, most developmental authorities argue against their use because they do not foster the internalization of rules of behavior and may legitimize violence.

Gershoff ET, Grogan-Kaylor A. Spanking and child outcomes: old controversies and new meta-analyses. *J Fam Psychol.* 2016;30(4):453–469.
Larsen MA, Tentis E. The art and science of disciplining children. *Pediatr Clin North Am.* 2003;50(4):817–840.

33. How valid is the proverb "spare the rod and spoil the child" as a defense for corporal punishment?

The actual biblical proverb (Proverbs 13:24) reads, "He who spares the rod hates his son, but he who loves him is careful to discipline him." Although the proverb has often been used as a justification for spanking, in actuality it does not refer to specific discipline strategies, but rather to the need for love and discipline. In addition, the rod may refer to the shepherd's staff, which was used to guide—rather than hit—sheep.

Carey TA. Spare the rod and spoil the child: is this a sensible justification for the use of punishment in child rearing? *Child Abuse Negl.* 1994;18(12):1005–1010.

34. Is physical injury a concern in children with head banging?

Head banging, which is a common problem that occurs in 5% to 15% of normal children, rarely results in physical injury. When injury does occur, it is usually in children with autism or other developmental disabilities. Normal children often show signs of bliss as they bang away, and the activity usually resolves by the time the child is 4 years old. (It may resume spontaneously during pediatric board examinations.)

35. What is the difference between a "blue" breath-holding spell and a "white" breath-holding spell?

Both are nonepileptic, paroxysmal syncopal attacks with involuntary cessation of breathing that occur in up to 4% of children between the ages of 6 months and 4 years. Eighty percent to 90% occur before 18 months of age.

- *"Blue" or cyanotic spell*: More comm [illegible] Vigorous crying provoked by physical or emotional upset leads to apnea at the end of expiration. This i[illegible]d by cyanosis, opisthotonus, rigidity, and, ultimately, loss of tone.

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Brief convulsive jerking may occur. The episode lasts from 10 to 60 seconds. A short period of sleepiness may ensue.

- *"White" or pallid spell:* More commonly precipitated by an unexpected event that frightens the child. Crying is limited or absent. Breath holding and loss of consciousness occur simultaneously. On testing, children prone to these spells demonstrate increased responsiveness to vagal maneuvers. This parasympathetic hypersensitivity may cause cardiac slowing, diminished cardiac output, and diminished arterial pressure, which result in a pale appearance.

36. When should a diagnosis of seizure disorder be considered rather than a breath-holding spell?

- Precipitating event is minor or nonexistent
- History of no or minimal crying or breath holding
- Episode lasts >1 minute
- Period of postepisode sleepiness lasts >10 minutes
- Convulsive component of episode is prominent and occurs before cyanosis
- Occurs in child <6 months or >4 years old
- Associated with incontinence

37. Does treatment with iron decrease the frequency of breath-holding spells?

In the 1960s, it was observed that children with breath-holding spells had lower hemoglobin levels than controls. Treatment with iron has decreased the frequency of breath-holding spells in some children, most notably those with iron-deficiency anemia. A complete blood count and ferritin level should be considered as part of the evaluation in patients with breath-holding spells. Interestingly, some of the children whose breath-holding spells respond to iron are not anemic, and the mechanism by which iron decreases breath-holding spells is not known.

Leung AKC, Leung AAM, Wong AHC, et al. Breath-holding spells in pediatrics: a narrative review of the current evidence. *Curr Pediatr Rev.* 2019;15(1):22–29.

Zehetner AA, Orr N, Buckmaster A, et al. Iron supplementation for breath-holding attacks in children. *Cochrane Database of Syst Rev.* 2010;5:CD008132.

38. When does prolonged thumb-sucking warrant intervention?

If frequent thumb-sucking persists in a child who is >4 to 5 years or in whom permanent teeth have begun to erupt, treatment is usually indicated. Persistent thumb-sucking after the eruption of permanent teeth can lead to malocclusion.

39. What treatments are used for thumb-sucking?

Treatment commonly has two components: (1) physical modifications, such as an application of a substance with an unpleasant taste, at frequent intervals (such products are commercially available) and/or use of a thumb splint or glove for nighttime sucking; and (2) behavior modification with positive reinforcement (small rewards) given when a child is observed not sucking his or her thumb. Occlusive dental appliances, which interfere with the seal required for sucking, are generally not needed, but are effective when utilized.

Borrie FR, Bearn DR, Innes NP, et al. Interventions for the cessation of non-nutritive sucking habits in children. *Cochrane Database Syst Rev.* 2015;3:CD008694.

40. When should "toilet training" be started?

When a child has **language readiness** (use of two-word phrases and two-step commands), **understands the cause and effect of toileting**, seems to **desire independence** without worsening oppositional behaviors, and has **sufficient motor skills and body awareness**, training can be begun. The physical prerequisite of the neurologic maturation of bladder and bowel control usually occurs between 18 and 30 months of age. The child's emotional readiness is often influenced by his or her temperament, parental attitudes, and parent–child interactions. The "potty chair" is typically introduced when the child is between 2 and 3 years old. In the United States, about one-fourth of children achieve daytime continence by 2 years and 98% by 3 years. There are distinct racial disparities regarding parental beliefs. Black parents believe training should be initiated around 18 months compared with 25 months for white parents. Additionally, initiation of toilet training varies considerably by culture and country.

Jacob H, Grodinski B, Fertleman C. Fifteen-minute consultation: problems in the healthy child—toilet training. *Arch Dis Child Educ Pract Ed.* 2016;101(3):119–123.

Horn IB, Brenner R, Rao M, et al. Beliefs about the appropriate age for initiating toilet training: are there racial and socioeconomic differences? *J Pediatr.* 2006;149(2):165–168.

41. Are girls or boys toilet trained earlier?

On average, **girls** are toilet trained earlier than boys. With regard to most other developmental milestones during the first years of life, however, there [illegible] not appear to be significant sex differences (i.e., in walking or running, sleep patterns, or verbal ability). Girls [illegible] show more rapid bone development.

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42. Are we toilet training children at an earlier age?

On the contrary, there has been a steady increase in the attainment of bowel and bladder continence from approximately 18 months of age in the 1940s to 24 months in the 1950s to 36 to 39 months in the late 1990s. Reasons are unclear, but later initiation of the process and increased incidences of stool toileting refusal and constipation may explain some of the trend.

Blum NJ, Taubman B, Nemeth N. Why is toilet training occurring at older ages? A study of factors associated with later training. *J Pediatr.* 2004;145(1):107–111.

CRANIAL DISORDERS

43. How many fontanels are present at birth?

Although six fontanels are present at birth (two anterior lateral, two posterior lateral, one anterior, and one posterior), only two (the anterior and posterior fontanels) are usually palpable on physical examination (Fig. 2.1).

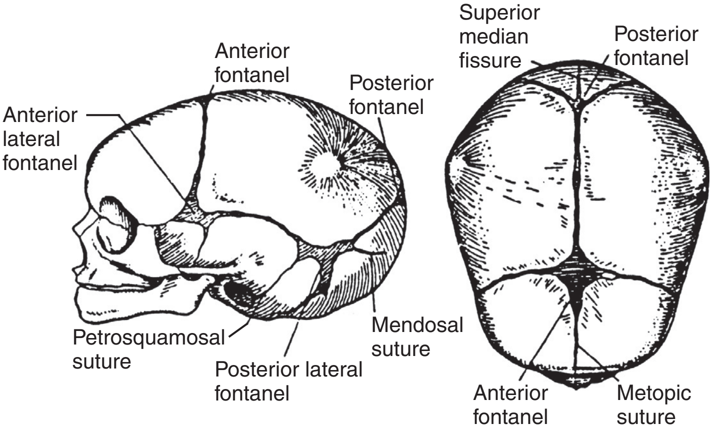

Fig. 2.1 The cranium at birth, showing major sutures and fontanels. No attempt is made to show molding or overlapping of bones, which sometimes occurs at birth. (From Silverman FN, Kuhn JP, eds. *Caffey's Pediatric X-ray Diagnosis.* 9th ed. St. Louis, MO: Mosby; 1993:5.)

44. When does the anterior fontanel close?

On the basis of studies using physical examination, classic teaching indicated between 10 and 14 months. However, computed tomography (CT) scans indicate that closure is quite variable and occurs later than previously thought. Only 16% of anterior fontanels are closed at 10 months, 50% at 16 months, and 88% at 20 months. Thus about 10% of normal infants may not have complete closure until 20 to 24 months of age. Of note, 3% to 5% of normal infants have closure at 5 to 6 months.

Pindrik F, Ye X, Ji BG, et al. Anterior fontanelle closure and size in full-term children based on head computed tomography. *Clin Pediatr.* 2014;53(12):1149–1157.

45. Which conditions are most commonly associated with premature or delayed closure of the fontanel?

- *Premature closure:* Microcephaly, high calcium–to–vitamin D ratio in pregnancy, craniosynostosis, hyperthyroidism, or variation of normal
- *Delayed closure:* Achondroplasia, Down syndrome, increased intracranial pressure, familial macrocephaly, rickets, or variation of normal

46. When is an anterior fontanel too big?

The size of the fontanel can be calculated using the formula: (length + width) / 2, where length equals anterior-posterior dimension and width equals transverse dimension. However, there is wide variability in the normal size range of the anterior fontanel. Mean fontanel size on day 1 of life is 2.1 cm, with an upper limit of normal of 3.6 cm in white infants and 4.7 cm in black infants. These upper limits may be helpful for identifying disorders in which a large fontanel may be a feature (e.g., hypothyroidism, hypophosphatasia, skeletal dysplasias, increased intracranial pressure). Of note is that the posterior fontanel is normally about the size of a fingertip or smaller in 97% of full-term newborns.

Kiesler J, Ricer R. The anterior fontanel. *Am Fam Pl[illegible]ician.* 2003;67(12):2547–2552.

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47. What are the types of primary craniosynostosis?

Craniosynostosis is the premature fusion of various cranial suture lines that results in the ridging of the sutures, asymmetric growth, and deformity of the skull. Suture lines (with resultant disorders listed in parentheses) include sagittal (scaphocephaly or dolichocephaly); coronal (brachycephaly); unilateral, coronal, or lambdoidal (plagiocephaly); and metopic (trigonocephaly). Multiple fused sutures can result in a high and pointed skull (oxycephaly or acrocephaly) (Fig. 2.2).

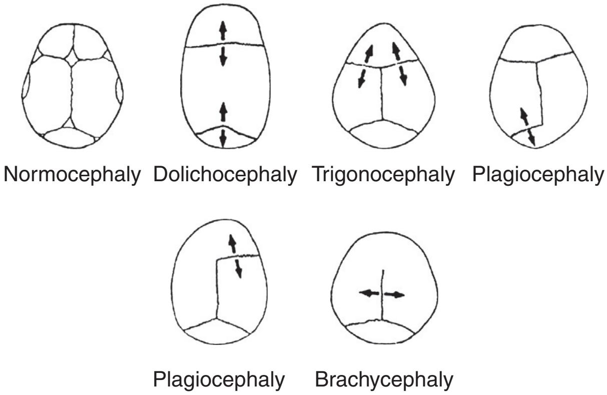

Fig. 2.2 Types of primary craniosynostosis.

48. What is the most common type of primary craniosynostosis?

Sagittal (60%); coronal synostosis accounts for 20% of cases.

49. What causes craniosynostosis?

Most cases of isolated craniosynostosis have no known etiology. *Primary* craniosynostosis may be observed as part of craniofacial syndromes, including Apert, Crouzon, and Carpenter syndromes. *Secondary* causes can include abnormalities of calcium and phosphorus metabolism (e.g., hypophosphatasia, rickets), hematologic disorders (e.g., thalassemia), mucopolysaccharidoses, and hyperthyroidism. Inadequate brain growth (e.g., microcephaly) can lead to craniosynostosis.

Williams H. Lumps, bumps and funny shaped heads. *Arch Dis Child Educ Pract Ed.* 2008;93(4):120–128.

50. What is positional or deformational plagiocephaly?

Since the implementation of the “back-to-sleep” program by the AAP in 1992 to reduce the risk for sudden infant death syndrome (SIDS), an estimated 13% to 20% of infants develop occipital flattening (posterior or lambdoidal plagiocephaly) due to transient calvarial deformation from prolonged supine sleeping positions. The condition can be prevented by varying the infant’s head position during sleep and feeding and by observing prone positioning (“tummy time”) for at least 5 minutes daily during the first 6 weeks of life. Therapy for severe cases consists of repositioning; physiotherapy; and, rarely, surgery. Helmet therapy, although widely used, has not been shown to be effective in one randomized study.

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van Wijk RM, van Vlimmeren LA, Groothuis-Oudshoorn CGM, et al. Helmet therapy in infants with positional skull deformation: randomised controlled trial. *BMJ.* 2014;348:g2741.

American Academy of Pediatrics Committee on Practice and Ambulatory Medicine. Prevention and management of positional skull deformities in infants. *Pediatrics.* 2011;128(6):1236–1241.

51. How is positional plagiocephaly differentiated from plagiocephaly caused by craniosynostosis?

Synostotic lambdoidal plagiocephaly is much rarer. It is usually associated with ridging of the involved suture lines, and it causes a different pattern of frontal bossing and ear displacement when the infant’s head is viewed from above (Fig. 2.3).

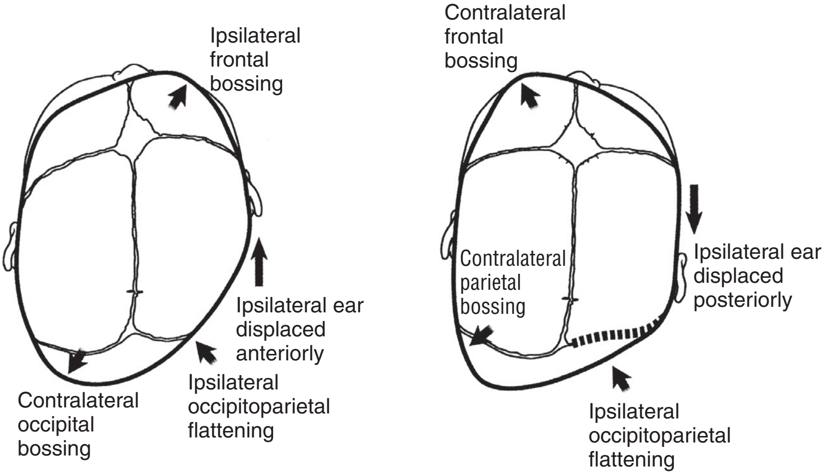
Ipsilateral frontal bossing
Ipsilateral ear displaced anteriorly
Ipsilateral occipitoparietal flattening
Contralateral occipital bossing
Contralateral frontal bossing
Ipsilateral ear displaced posteriorly
Contralateral parietal bossing
Ipsilateral occipitoparietal flattening

Fig. 2.3 Factors distinguishing *(left)* positional plagiocephaly from *(right)* lambdoidal craniosynostosis. (From Kabbani H, Raghuveer TS. Craniosynostosis. *Am Fam Physician.* 2004;69:2866.)

52. What conditions are associated with skull softening?

- Cleidocranial dysostosis
- Craniotabes
- Lacunar skull (associated with spina bifida and major CNS anomalies)
- Osteogenesis imperfecta
- Multiple wormian bones (associated with hypothyroidism, hypophosphatasia, and chronic hydrocephalus)
- Rickets

53. What is the significance of craniotabes?

In this condition, abnormally soft, thin skull bones buckle under pressure and recoil like a ping-pong ball. It is best elicited on the parietal or frontal bones and is often associated with rickets in infancy. It may also be seen in hypervitaminosis A, syphilis, and hydrocephalus. Craniotabes may be a normal finding during the first 3 months of life.

54. What evaluations should be done in a child with microcephaly?

The extent of evaluation depends on various factors: prenatal versus postnatal acquisition, presence of minor or major anomalies, developmental problems, and neurologic abnormalities. The diagnosis can be as straightforward as a simple familial variant (autosomal dominant) in a child with normal intelligence, or it can range to a variety of conditions associated with abnormal brain growth (e.g., intrauterine infections, heritable syndromes, chromosomal abnormalities). Evaluation may include the following:

- Parental head-size measurements
- Ophthalmologic evaluation (abnormal optic nerve or retinal findings may be found in various syndromes)
- Genetic testing (e.g., karyotype, chromosomal microarray analysis)
- Neuroimaging (cranial MRI or CT to evaluate for structural abnormalities or intracranial calcifications)
- Metabolic screening
- Cultures and serology if suspected intrauterine infection (e.g., cytomegalovirus [CMV], Zika virus)

Devakumar D, Bamford A, Ferreira MU, et al. Infectious causes of microcephaly: epidemiology, pathogenesis, diagnosis and management. *Lancet Infect Dis.* 2018;18(1):e1–e13.

Von der Hagen M, Pivarcsi M, Liebe J, et al. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. *Dev Med Child Neuro.* 2014;56(8):732–741.

55. What are the three main general causes of macrocephaly?

- **Increased intracranial pressure:** Caused by dilated ventricles (e.g., progressive hydrocephalus of various causes), subdural fluid collections, intracranial tumors, or idiopathic intracranial hypertension (i.e., pseudotumor cerebri)
- **Thickened skull:** Caused by cranioskeletal dysplasias (e.g., osteopetrosis) and various anemias
- **Megalencephaly** (enlarged brain): May be familial or syndromic (e.g., Sotos syndrome) or caused by storage diseases, leukodystrophies, or neurocutaneous disorders (e.g., neurofibromatosis)

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DENTAL DEVELOPMENT AND DISORDERS

56. When do primary and permanent teeth erupt?

Mandibular teeth usually erupt first. The central incisors appear by the age of 5 to 7 months, with about one new tooth per month thereafter until 23 to 30 months, at which time the second molars (and thus all 20 primary or deciduous teeth) are in place. Of the 32 permanent teeth, the central incisors erupt first between 5 and 7 years, and the third molars are in place by 17 to 22 years.

57. What is the significance of natal teeth?

Occasionally, teeth are present at birth *(natal teeth)* or erupt within 30 days after birth *(neonatal teeth)*. When x-rays are taken, 95% of natal teeth are primary incisors and 5% are supernumerary teeth or extra teeth. Very sharp teeth that can cause tongue lacerations and very loose teeth that can be aspirated should be removed. Females are affected more commonly than males, and the prevalence is 1 in 2000 to 3500. Most cases are familial and without consequence, but natal teeth can be associated with genetic syndromes, including the Ellis-van Creveld and Hallermann-Streiff syndromes.

58. How common is the congenital absence of teeth?

The congenital absence of primary teeth is very rare, but up to 25% of individuals may have an absence of one or more third molars, and up to 5% may have an absence of another secondary or permanent tooth (most commonly the maxillary lateral incisors and mandibular second premolar).

59. What are mesiodentes?

These are **peg-shaped supernumerary teeth** that occur in up to 5% of individuals, and they are most commonly situated in the maxillary midline. They should be considered for removal because they interfere with the eruption of permanent incisors.

60. What is the significance of an infant presenting with a single central upper tooth?

A solitary median maxillary central incisor (Fig. 2.4) may be associated with developmental defects, short stature (due to growth hormone deficiency), mild craniofacial dysmorphology, and intellectual disability. It is another example of a midline defect having potential significance regarding accompanying CNS abnormalities.

Viana ES, Kramer PF, Closs LQ, Scalco G. Solitary median maxillary central incisor syndrome and holoprosencephaly: a case report. *Pediatr Dent.* 2010;32(5):424–427.

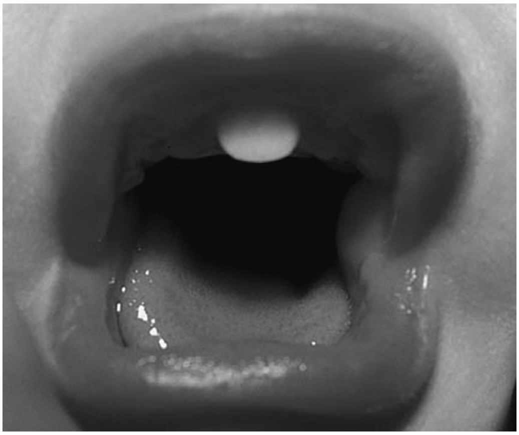

Fig. 2.4 Central maxillary incisor. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis.* 5th ed. Philadelphia, PA: Mosby Elsevier; 2011:353.)

61. Why do we have wisdom teeth?

This third set of molars is felt to be an evolutionary product of the early ancestral diet of coarse, rough food such as leaves, roots, and nuts, which required greater grinding power as well as a broader jaw. As diets changed over the millennia and human jaws evolved to become smaller, space for wisdom teeth became compromised. Wisdom teeth are now considered vestigial teeth. It is estimated that 20% and 25% are born with only one to three wisdom teeth and 35% are born without any, often the result of genetic influences. The third set of molars were called *wisdom teeth* because they appeared later in life (17 to 24 years of age), when most individuals were presumably wiser.

American Association of Oral and Maxillofacial Surgeons. www.aaoms.org. Accessed July 16, 2019.

62. When is it wise to remove wisdom teeth?

The third of three sets of upper and lower molars typically erupt between ages 17 and 24 years. Incomplete eruption (or impaction) commonly occurs, which can predispose to infection or to misalignment that can damage nearby teeth (Fig. 2.5). Extraction, when necessary, is most ideal in late adolescence when roots may not be completely developed. A decision to prophylactically remove asymptomatic, disease-free wisdom teeth due to an increased risk for future complications is controversial.

American Association of Oral and Maxillofacial Surgeons. www.aaoms.org. Accessed July 16, 2019.

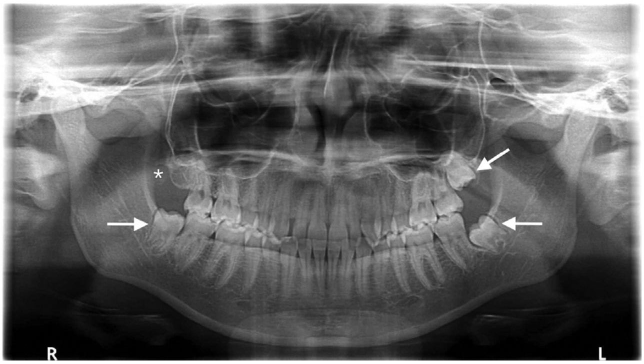

Fig. 2.5 Dental x-ray in an older adolescent demonstrating three erupting/impacted wisdom teeth with some malalignments *(arrows)*. Note that the patient lacks a fourth wisdom tooth *(asterisk)*.

63. What is a ranula?

A large **mucocele,** usually bluish, painless, soft, and unilateral, that occurs under the tongue (Fig. 2.6). Most of these self-resolve. If a patient has a large one, surgical marsupialization can be done. If the ranula is recurrent, excision may be needed.

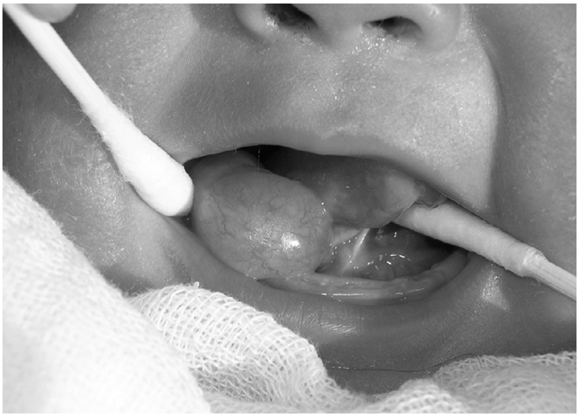

Fig. 2.6 Sublingual ranula of right floor mouth in 1-month infant. (From Zhi K, Wen Y, Ren W, Zhang Y. Management of infant ranula. *Int J Pediatr Otolaryngol.* 2008;72:823–826.)

64. Where are Epstein pearls located?

These white, superficial, mobile nodules are usually midline and often paired on the hard palate in many newborns. They are keratin-containing cysts that are asymptomatic, do not increase in size, and usually exfoliate spontaneously within a few weeks.

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65. What is the most common chronic disease of childhood?

Dental caries affects nearly half of children ages 2 to 11 years, which is 2.5 times the rate of obesity, 4 times the rate of asthma, and 7 times the rate of allergic rhinitis. By 17 years of age, only 15% to 20% of individuals are free from dental caries, and the average child has eight decayed, missing, or filled tooth surfaces. Prevention of dental caries involves a decrease in the frequency of tooth exposure to carbohydrates (frequency is more important than total amount), the use of fluoride supplements at age 6 months for children whose water supply is deficient in fluoride, application of fluoride varnish to all infants and children beginning at the age of primary tooth eruption, increased brushing of the teeth, and the use of dental sealants.

Moyer V. Prevention of dental caries in children from birth through age 5 years: US Preventive Services Task Force recommendation statement. *Pediatrics.* 2014;133(6):1102–1111.

66. What is milk-bottle caries?

Frequent contact of cariogenic liquids (e.g., milk, formula, breast milk, juice) with teeth, as occurs in infants who fall asleep with a bottle or who are breastfed frequently at night after the age of 1 year ("nursing caries"), has been associated with a significant increase in the development of caries (Fig. 2.7). The AAP recommends that infants not be put to sleep with a bottle (unless it is filled with water), that nocturnal ad lib breastfeeding be limited as dental development progresses, and that cup feedings be introduced when the child is 1 year old.

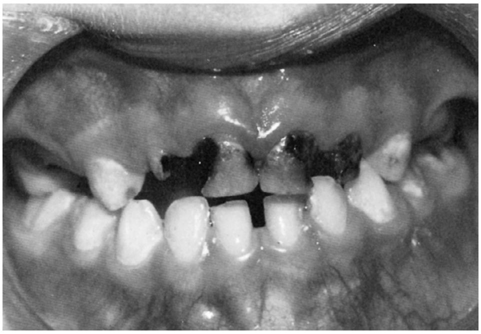

Fig. 2.7 Classic nursing bottle decay involving the maxillary anterior teeth. Mandibular incisors are protected by the tongue during feeding and are usually caries free. (From Gessner IH, Victorica BE. *Pediatric Cardiology: A Problem-Oriented Approach.* Philadelphia, PA: W. B. Saunders; 1993:232.)

67. How does fluoride minimize the development of dental caries?

- Topical fluoride from toothbrushing is thought to increase the remineralization of enamel.
- Bacterial fermentation of sugar into acid plays a major role in the development of caries, and fluoride inhibits this process.
- As teeth are developing, fluoride incorporates into the hydroxyapatite crystal of enamel, thereby making it less soluble and less susceptible to erosion.

Pollick H. The role of fluoride in the prevention of tooth decay. *Pediatr Clin North Am.* 2018;65(5):923–940.

68. What is fluorosis?

Exposure to excessive levels of fluoride during tooth development, primarily in a patient younger than 8 years, can damage enamel, causing changes that range from mild (lacy white markings) to severe (pitting, mottling, striations).

69. How long should fluoride supplementation be continued?

Fluoride supplementation should continue until a child is 14 to 16 years old, when the third molar crowns are completely calcified.

KEY POINTS: DENTAL PROBLEMS

1. Prolonged pacifier use beyond the age of 18 months can result in oral and dental distortions.
2. Dental caries is the most common chronic disease of childhood.
3. Appropriate use of fluoride and dental sealants could prevent caries in most children.
4. Use of formula or breastfeeding at bedtime after dental eruption leads to higher incidences of caries.
5. Excessive fluoride is associated initially with a white, speckled, or lacy appearance of the enamel.
6. Necessity for and timing of extraction of asymptomatic wisdom teeth are controversial.

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70. How effective are dental sealants at preventing cavities?

Dental sealants may reduce the development of caries by up to 80% compared with rates in untreated teeth. Although fluoride acts primarily by protecting smooth surfaces, dental sealants (commonly bisphenol A and glycidyl methacrylate) act by protecting the pits and fissures of the surface, especially in posterior teeth. Reapplication may be needed every 2 years. As a preventive dental procedure, it is relatively underused.

71. How common is gingivitis in children?

Gingivitis is **extremely common**, affecting nearly 50% of children. The disorder is usually painless and is manifested by the bluish-red discoloration of gums, which are swollen and bleed easily. The cause is bacteria in plaque deposits between teeth; the cure is improved dental hygiene and daily flossing.

72. What is the largest health-related expense before adulthood for normally developing children?

Dental braces. More than 50% of children have dental malocclusions that could be improved with treatment, but only 10% to 20% have severe malocclusions that require treatment. For others, the costs and benefits of braces need to be weighed individually. Besides the financial expense, the costs of braces include physical discomfort and some increases in the risk for tooth decay and periodontal disease.

DEVELOPMENTAL ASSESSMENT

73. What aspects of development are typically monitored?

- Motor skills (gross and fine motor)
- Speech and language
- Activities of daily living (social and personal)
- Cognition

Bellman M, Byrne O, Sege R. Developmental assessment of children. *BMJ.* 2013;346:e8687.

74. What are primitive reflexes?

Primitive reflexes are **automatisms** that are usually triggered by an external stimulus. They are thought to emanate from primitive regions of the CNS: the spine, the inner ear labyrinths, and the brainstem. Examples are rooting, which is triggered by touching the corner of the mouth, and the asymmetric tonic neck reflex (ATNR), which is triggered by rotating the head. Some reflexes (e.g., rooting, sucking, and grasp) have survival value. Others, such as the ATNR or the tonic labyrinthine reflex, have no obvious purpose. Placing and stepping reflexes usually disappear by 2 months. Moro and grasp reflexes and the ATNR usually disappear by 5 months.

75. What are the three most common primitive reflexes?

- **ATNR:** In a calm supine infant, turning of the head laterally results in relative extension of the arm and leg on the side of the turn and flexion of both on the side away from the turn (the “fencer” position).
- **Moro reflex:** Sudden neck extension results in extension, abduction, and then adduction of the upper extremities with flexion of fingers, wrists, and elbows.
- **Tonic labyrinthine reflex:** In an infant who is being held suspended in the prone position, flexion of the neck results in shoulder protraction and hip flexion, whereas neck extension causes shoulder retraction and hip extension.

Zafeiriou DI. Primitive reflexes and postural reactions in the neurodevelopmental examination. *Pediatr Neurol.* 2004;31(1):1–8.

76. At what age do children develop handedness?

Usually by **18 to 24 months**. Hand preference is usually fixed by the time a child is 5 years old. Handedness before 1 year may be indicative of a problem with the nonpreferred side (e.g., hemiparesis, brachial plexus injury).

77. What percentage of children are left-handed?

Various studies put the prevalence at **between 7% and 10%.** However, in former premature infants without cerebral palsy, the rate increases to 20% to 25%. Although antecedent brain injury has been hypothesized to account for this increase in prevalence of left-handedness, studies of unilateral intraventricular hemorrhage and handedness have not demonstrated a relationship. Of note is that animals such as mice, dogs, and cats show paw preferences, but, in these groups, 50% prefer the left paw and 50% prefer the right paw.

Marlow N, Roberts BL, Cooke RW. Laterality and prematurity. *Arch Dis Child.* 1989;64(12):1713–1716.

78. Are there ethnic differences in development in the first year of life?

Yes. Even after correcting for potential variables such as social, economic, environmental, and household characteristics, ethnic differences in the attainment of developmental milestones occur. A large-scale population-based study in the United Kingdom found that Indian, black Caribbean, and black African children were much less likely to show delays in gross motor milestones compared with white children.

Kelly Y, Sacker A, Schoon I, et al. Ethnic differences in achievement of developmental milestones by 9 months of age: the Millennium Cohort Study. *Dev Med Child Neurol.* 2006;48(10):825–830.

79. What are the major developmental landmarks for motor skills during the first 2 years of life?

See Table 2.1.

Table 2.1 Major Developmental Landmarks for Motor Skills

DEVELOPMENTAL LANDMARK	AGE RANGE (MONTHS)
Major Gross Motor	
Steadiness of head when placed in supported position	1-4
Sits without support for >30 seconds	5-8
Cruises or walks holding on to things	7-13
Stands alone	9-16
Walks alone	9-17
Walks up stairs with help	12-23
Major Fine Motor	
Grasp	2-4
Reach	3-5
Transfers objects from hand to hand	5-7
Fine pincer grasp with index finger and thumb apposition	9-14
Spontaneous scribbling	12-24

80. How valuable is the timing of crawling as a marker of development?

Crawling is one of the least valuable milestones because there is enormous variability in the timing of crawling. A significant percentage of normal infants never crawl before walking.

Wong K. Crawling may be unnecessary for normal child development. *Scientific American.* 2009;301:11.

81. What are major red flags that a child's development is abnormal?

Presence of:

- Loss of developmental skills at any age
- Parental concerns about a child's vision or ability to follow objects
- Persistently low muscle tone or floppiness
- No speech (or other efforts to communicate) by 18 months
- Asymmetry of movements
- Persistent toe walking
- Evidence of microcephaly or macrocephaly, particularly if discordant with parental head circumference percentiles

Inability to:

- Sit unsupported by 12 months
- Walk by 18 months (boys) or 2 years (girls)
- Walk other than on tiptoes
- Run by 2.5 years
- Reach for objects by 6 months (corrected for prematurity, if applicable)
- Point at objects to demonstrate to others by 2 years

Bellman M, Byrne O, Sege R. Developmental assessment of children. *BMJ.* 2013;346:e8692.

82. What features suggest a possible metabolic cause for disordered development?

- Parental consanguinity
- Family history of unexplained death in childhood
- Progressive or intermittent symptoms (such as vomiting), which are unexplained
- Symptom-free intervals
- Slowing of developmental skill acquisition
- Loss of skills
- Evidence of encephalopathy (e.g., personality changes, periods of lethargy)
- Specific phenotype
- Coarse facial features
- Organomegaly

Horridge KA. Assessment and investigation of the child with disordered development. *Arch Dis Child Educ Pract Ed.* 2011;96(1):9–20.

83. Do infant walkers promote physical strength or development of the lower extremities?

No. On the contrary, published data confirm that infants in walkers actually manifest mild but statistically significant gross motor delays. Infants with walkers were found to sit and crawl later than those without walkers. However, most walk unaided within a normal time frame. Safety hazards can include head trauma, fractures, burns, finger entrapments, and dental injuries. Most of the serious injuries involve falls down stairs. Because of the injury risks, the AAP recommends a ban on the manufacture and sale of infant walkers.

Sims A, Chounthirath T, Yang J, et al. Infant walker-related injuries in the United States. *Pediatrics.* 2018;142(4):e20174332.

Pin T, Eldridge B, Galea MP. A review of the effects of sleep position, play position and equipment use on motor development in infants. *Dev Med Child Neuro.* 2007;49(11):858–867.

84. Do twins develop at a rate that is comparable to infants of single birth?

Twins exhibit **significant verbal and motor delay** during the first year of life. The difficulty lies not in the lack of potential but in the relative lack of individual stimulation. In general, children who are more closely spaced in a family have slower acquisition of verbal skills. Twins with significant language delay or with excessive use of “twin language” (language understood only by the twins themselves) may be candidates for interventional therapy.

85. Do premature infants develop at the same rate as term infants?

For the most part, premature infants do develop at the same rate as term infants. In ongoing developmental assessments, they eventually “catch up” to their chronologic peers, not by accelerated development, but rather through the arithmetic of time. As they age, their degree of prematurity (in months) becomes less of a percentage of their chronologic age. Early in life, the extent of prematurity is key and must be considered during developmental assessments. Such “correction factors” are generally unnecessary after the age of 2 to 3 years, depending on the degree of prematurity.

86. When can an infant smell?

The sense of smell is present **at birth**. Newborn infants show preferential head turning toward gauze pads soaked with their mother’s milk as opposed to the milk of another woman. The same holds for axillary odor. In one study, infants exposed to familiar odors before heel-stick procedures had lower pain responses.

Marin MM, Rapisardi G, Tani F. Two-day-old newborn infants recognise their mother by her axillary odour. *Acta Paediatr.* 2015;104(3):237–240.

Goubet N, Strasbaugh K, Chesney J. Familiarity breeds content? Soothing effect of a familiar odor on full-term newborns. *J Dev Behav Pediatr.* 2007;28(3):189–194.

87. What are the best measures of cognitive development?

Ideally, cognitive development should be assessed in a fashion that is free of motor requirements. **Receptive language** is the best measure of cognitive function. Even an eye blink or a voluntary eye gaze can be used to assess cognition independently of motor disability. Adaptive skills such as tool use (e.g., spoon, crayon) are also useful, although they may be delayed because of purely motoric reasons. Gross motor milestones such as walking raise concerns about intellectual disability if they are delayed, but normal gross motor milestones cannot be used to infer normal cognitive development.

88. What do the stages of play tell us about a child’s development?

A well-taken history of a child’s play is a valuable adjunct to more traditional milestones, such as language and adaptive skills (Table 2.2).

Table 2.2 Play Activity and Child Development

AGE RANGE (MONTHS)	PLAY ACTIVITY	UNDERLYING SKILLS
3	Midline hand play	Sensorimotor; self-discovery
4-5	Bats at objects	Ability to affect environment
6-7	Directed reaching; transfers	
7-9	Banging and mouthing objects	
12	Casting ("I throw it down, and you pick it up for me"); explores objects by visual inspection and handling rather than orally	Object permanence; social reciprocity; use of pointing, joint attention (eye gaze), and simple language to effect response in caregiver
16-18+	Stacking and dumping; exploring; lids; light switches; simple mechanical toys (jack-in-the-box; shape ball)	Means-ends behavior: experimenting with causality
24	Imitative play ("helping" with the dishes; doll play with a physical doll)	Language and socialization; development of "inner language"
36	Make-believe play (e.g., doll play with a pillow to represent the doll)	Distinguish between "real" and "not real"
48	Simple board games, rule-based playground games (e.g., "tag")	Concrete operations (Piaget)

89. What can one learn about a child's developmental level with regard to the use of a crayon?

A lot. At less than 9 months, the infant will use the crayon as a teething object. Between 10 and 14 months, the infant will make marks on a piece of paper, almost as a by-product of holding the crayon and "banging" it against the paper. By 14 to 16 months, the infant will make marks spontaneously, and by 18 to 20 months, he or she will make marks with vigorous scribbling. By 20 to 22 months, an infant will begin copying specific geometric patterns as presented by the examiner (Table 2.3). The ability to execute these figures requires visual-perceptual, fine-motor, and cognitive abilities. Delay in the ability to complete these tasks suggests difficulty with one or more of these underlying streams of development.

Table 2.3 Crayon Use and Development Level

AGE	TASK
20-22 mo	Alternates from scribble to stroke on imitation of examiner
27-30 mo	Alternates from horizontal to vertical on imitation of examiner
36 mo	Copies circle from illustration
3 yr	Copies cross
4 yr	Copies square
5 yr	Copies triangle
6 yr	Copies "Union Jack"

90. What is the value of the Goodenough-Harris drawing test?

This "draw a person" test is a screening tool used to evaluate a child's cognition and intellect, visual perception, and visual-motor integration. The child is asked to draw a person, and a point is given for each body part drawn with pairs (e.g., legs) that is considered one part. An average child who is 4 years and 9 months old will draw a person with three parts; most children by the age of 5 years and 3 months will draw a person with six parts.

91. What are key physical examination features in the evaluation of a child with possible developmental delay?

- **Head circumference:** possible microcephaly or macrocephaly
- **Dysmorphic features:** possible genetic, metabolic, or syndromic conditions
- **Skin abnormalities** (e.g., café au lait spots, neurofibromas): possible neurocutaneous syndrome
- **Observations of movements** (e.g., unsteadiness, weakness, spasticity): possible underlying neurologic disorder
- **Assessment of tone, strength, and reflexes:** possible underlying neurologic disorder
- **Eye examination** (e.g., nystagmus, cataract): possible disorder of vision due to neurologic disorder
- **Liver size** (e.g., hepatomegaly): possible metabolic disorder

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Bellman M, Byrne O, Sege R. Developmental assessment of children. *BMJ.* 2013;346:e8687.

92. In infants and children with unexplained global developmental delay or intellectual disability, what is the diagnostic yield of genetic testing?

In children for whom an initial history and physical examination do not uncover an underlying cause of intellectual disability or global developmental delay, 15% to 20% have genetic abnormalities with chromosomal microarray analysis, which has been recommended as the first-line clinical diagnostic test due to its capability of detecting small genetic deletions and duplications. Fragile X testing is also recommended to simultaneously be done, but its yield is lower (0.5% to 2%). Whole-exome sequencing and other next-generation sequencing panels of ID genes (with some panels encompassing analysis of >2000 genes) may increase the identification of pathogenic mutations to significantly higher percentages.

Pekeles H, Accogli A, Boudrahem-Addour N, et al. Diagnostic yield of intellectual disability gene panels. *Pediatr Neurol.* 2019;92:32–36.
Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Human Genetics.* 2010;86(5):749–764.

93. What factors increase the likelihood of finding a potentially progressive disease in patients with global delay?

- Affected family member
- Parental consanguinity
- Organomegaly
- Absent tendon reflexes

Fenichel GM. *Clinical Pediatric Neurology.* 6th ed. Philadelphia, PA: Elsevier; 2009:121.

INTELLECTUAL DISABILITY

94. Why was the term mental retardation changed to intellectual disability?

There was controversy that the term was stigmatizing and pejorative, and it is no longer used in clinical practice. DSM-5 replaced “mental retardation” with the designation “intellectual disability.” However, because of numerous statutes and programs that use the term *mental retardation* and thus carry legal ramifications, the change will likely be a gradual process.

Harris JC. New terminology for mental retardation in DSM-5 and ICD-11. *Curr Opin Psychiatry.* 2013;26(3):260–262.

95. How is intellectual disability defined?

The American Association on Intellectual and Developmental Disabilities defines intellectual disability as “a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. This disability originates before the age of 18.” Of note, *global development delay* is the preferred term for children <5 years with significant functional delay in two or more domains, which include motor, speech or language, cognition, social, and activities of daily living.

American Association on Intellectual and Developmental Disabilities. www.aaidd.org. Accessed January 5, 2020.

96. How is intelligence classified with IQ scores?

Most IQ tests are constructed to yield a mean IQ of 100 and a standard deviation of 15 points (Table 2.4).

Table 2.4 Construction of Intelligence Quotient Scores

INTELLIGENCE QUOTIENT	STANDARD DEVIATION	CATEGORY
>130	>+2	Very superior
116-130	+1 to +2	High average to superior
115-85	Mean ± 1	Average
84-70	−1 to −2	Low average to borderline ID
69-55	−2 to −3	Mild ID
54-40	−3 to −4	Moderate ID
39-25	−4 to −5	Severe ID
<25	<−5	Profound ID

ID, Intellectual disability.

97. What features can indicate cognitive problems in infants and young children?

In younger infants and toddlers, fine motor skill development and especially language development are the usual best correlates of cognitive achievement. As the child ages, the various milestones can be evaluated. Significant sequential delay should warrant referral for formal developmental testing to evaluate the possibility of intellectual disability (Table 2.5).

First LR, Palfrey JS. The infant or young child with developmental delay. *N Engl J Med.* 1994;330(7):478–483.

Table 2.5 Signs of Sequential Delay in Cognitive Achievement

2-3 mo	Not alerting to mother with special interest
6-7 mo	Not searching for dropped object
8-9 mo	No interest in peek-a-boo
12 mo	Does not search for hidden object
15-18 mo	No interest in cause-and-effect games
2 yr	Does not categorize similarities (e.g., animals versus vehicles)
3 yr	Does not know own full name
4 yr	Cannot pick shorter or longer of two lines
4.5 yr	Cannot count sequentially
5 yr	Does not know colors or any letters
5.5 yr	Does not know own birthday or address

98. Worldwide, what is the most common preventable cause of intellectual disability?

Iodine deficiency leads to maternal and fetal hypothyroxinemia during gestation, which causes brain injury. Severe endemic iodine deficiency can cause cretinism (characterized by deaf-mutism, severe intellectual deficiency, and often hypothyroidism) and may occur in 2% to 10% of isolated world communities. Moderate iodine deficiency, which is even more common, leads to milder degrees of cognitive impairment.

Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. *Lancet.* 2008;372(9645):1251–1262.
Cao XY, Jiang XM, Dou ZH, et al. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. *N Engl J Med.* 1994;331(26):1739–1744.

LANGUAGE DEVELOPMENT AND DISORDERS

99. What are average times for the development of expressive, receptive, and visual language milestones?

See Table 2.6.

Table 2.6 Development of Expressive, Receptive, and Visual Language

AGE (MONTHS)	EXPRESSIVE	RECEPTIVE	VISUAL
0-3	Coo	Alerts to voice	Recognizes parents; visual tracking
4-6	Monosyllabic babbling, laugh, "raspberry"	Turns to voice and sounds	Responds to facial expressions
7-9	Polysyllabic babbling; mama/dada, nonspecific	Recognizes own name; inhibits to command "No"	Imitates games (patty cake; peek-a-boo)
10-12	Mama/dada specific; first word other than mama/dada or names of other family members or pets	Follows at least 1 one-step command without a gestural cue (e.g., "Come here," "Give me")	Points to desired objects
16-18	Uses words to indicate wants	Follows many one-step commands; points to body parts on command	
22-24	Two-word phrases	Follows two-step commands	
30	Telegraphic speech	Follows prepositional commands	
36	Simple sentences		

100. What are signs of significantly delayed receptive and expressive speech warranting evaluation?

See Table 2.7.

American Speech-Language-Hearing Association. www.asha.org. Accessed July 16, 2019.

Table 2.7 Signs of Speech-Language Problems Absolutely Needing Further Evaluation

AT AGE (MONTHS)	RECEPTIVE	EXPRESSIVE
15	Does not look/point at 5 to 10 objects/ people named by parent	Not using three words
18	Does not follow simple commands ("roll the ball")	No use of single words (including mama, dada)
24	Does not point to pictures or body parts when they are named	Single-word vocabulary of ≤10 words
30	Does not verbally respond or nod/shake head to questions	Not using unique two-word phrases, including noun–verb combinations; unintelligible speech
36	Does not understand prepositions or action words; does not follow two-step directions	Vocabulary <200 words; does not ask for things by name; echolalia to questions; regression of language after acquiring two-word phrases

Data from Harlor ADB Jr, Bower C. Clinical report—hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics.* 2009;124(4):1252-1263; and Schum RL. Language screening in the pediatric office setting. *Pediatr Clin North Am.* 2007;54(3):432.

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101. Do deaf infants babble?

Yes. Babbling begins at about the same time in both deaf and hearing infants, but deaf infants stop babbling without the normal progression to meaningful communicative speech.

Locke JL. Babbling and early speech: Continuity and individual differences. *First Language.* 1989;9:191–205.

102. Screen time and digital media use: Friends or foes?

Screen time refers to time spent with any screen, including television, computer, tablet, or smartphone. *Digital media*, both social and interactive, allows user consumption and creation of content, often involving the Internet. Much of the debate centers on "how much is too much," as pediatric use is considerable. In younger children, although there is some evidence for enhanced learning from touchscreen devices, use of these devices reduces parental interaction, which can affect cognitive development, especially language and executive function. In older children, smartphone use and television viewing can displace reading time and exercise and are associated with less sleep. Although the AAP continues to recommend limitations on the amount of screen time for younger children—avoidance for <18 to 24 months, 1 hour per day for 2 to 5 years of age—there is an increased emphasis on viewing high-quality content that is not too fast-paced, not distracting, and absent of violent content. Increased parental co-viewing is also being advised. Social media use may raise confidence and self-esteem and strengthen relationships in some adolescents; however, heavy use can become addictive and distracting, restrict direct communication skills, and cultivate a view of high-risk behaviors as normative. Given the relatively recent nature of the expansion of screen time and of the interactive digital age, the long-term effects on all pediatric ages remain to be determined.

Reid Chassiakos YL, Radesky J, Christakis D, et al. Children and adolescents and digital media. *Pediatrics.* 2016;138(5):e20162593.
AAP Council on Communications and Media. Media and young minds. *Pediatrics.* 2016;138(5):e201162591.

103. At what age does a child's speech become intelligible?

Intelligibility increases by about 25% per year. A 1-year-old child has about 25% intelligibility, a 2-year-old has 50%, a 3-year-old has 75%, and a 4-year-old has 100%. Significantly delayed intelligibility should prompt a hearing and language evaluation.

104. What risk factors make hearing loss more likely in a newborn or young infant?

- Craniofacial anomaly
- Family history of permanent childhood hearing loss
- Head trauma requiring hospitalization
- In utero infections (such as CMV, herpes, rubella, syphilis, toxoplasmosis)
- Neonatal intensive care unit (NICU) care for >5 days
- Need for extracorporeal membrane oxygenation (ECMO) therapy
- Exposure to ototoxic medications (gentamicin, tobramycin, furosemide)
- Hyperbilirubinemia that required exchange transfusion
- Stigmata of a syndrome associated with hearing loss

Yelverton JC, Dominguez LM, Chapman DA, et al. Risk factors associated with unilateral hearing loss. *JAMA Otolaryngol Head Neck Surg.* 2013;139(1):59–63.

105. What causes flat tympanograms?

Tympanometry is an objective measurement of the compliance of the tympanic membrane and the middle ear compartment that involves varying the air pressure in the external ear canal from about −200 to +400 mm H_2O while measuring the reflected energy of a simultaneous acoustic tone. A normal tracing looks like an inverted "V" with the peak occurring at an air pressure of 0 mm H_2O; this indicates a functionally normal external canal, an intact tympanic membrane, and a lack of excess of middle ear fluid. Flat tympanograms occur with perforation of the tympanic membrane, occlusion of the tympanometry probe against the wall of the canal, obstruction of the canal by a foreign body or impaction by cerumen, or large middle ear effusion. Flat tympanograms due to middle ear effusion are usually associated with a 20- to 30-dB conductive hearing loss, although in occasional instances, the loss may be as great as 50 dB.

106. A toddler with a bifid uvula (Fig. 2.8) and hypernasal speech most likely has what condition?

Velopharyngeal insufficiency with a possible **submucosal cleft palate**. The velum (soft palate) moves posteriorly during swallowing and speech, thereby separating the oropharynx from the nasopharynx. Velopharyngeal insufficiency exists when this separation is incomplete, which may occur after cleft palate repair or adenoidectomy (usually transient). In severe cases, nasopharyngeal regurgitation of food may occur. In milder cases, the only manifestation may be hypernasal speech as a result of the nasal emission of air during phonation. If a bifid uvula is present, one should palpate the palate carefully for the presence of a submucous cleft. Also, visualization of the hard palate may reveal a lucency in the midline ("zona pellucida") due to muscular diastasis (separation).

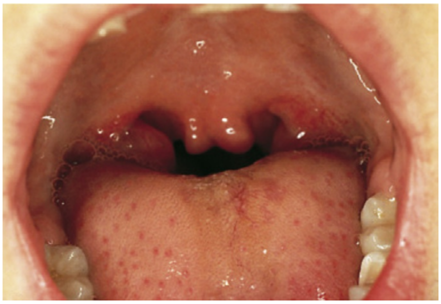

Fig. 2.8 Bifid uvula. (From Zitelli BJ, Davis HW. *Zitelli and Davis' Atlas of Pediatric Physical Diagnosis.* 7th ed. Philadelphia, PA: Elsevier: 2018:900.)

KEY POINTS: LANGUAGE DEVELOPMENT

1. Very red flags include no meaningful words by 18 months or no meaningful phrases by 2 years.
2. Intelligibility should increase yearly by 25%, from 25% at 1 year of age up to 100% at 4 years of age.
3. Stuttering is common in younger children, but beyond the age of 5 to 6 years, it warrants speech evaluation.
4. Autism, intellectual disability, and cerebral palsy can present with speech delay.
5. Evaluation of hearing is mandatory in any setting of significant speech delay.

107. When is stuttering abnormal?

Stuttering is a common characteristic of the speech of preschool children. However, most children do not persist with stuttering beyond 5 or 6 years of age. Preschoolers at increased risk for persistence of stuttering include those with a positive family history of stuttering and those with anxiety-provoking stress related to talking. A child older than 5 or 6 years who stutters should be referred to a speech-language pathologist for assessment and treatment.

National Stuttering Association. www.westutter.org. Accessed January 12, 2020.

108. What advice should be given to parents of a child who stutters?

- Do not give the child directives about how to deal with his or her speech (e.g., "Slow down" or "Take a breath").
- Provide a relaxed, easy speech model in your own manner of speaking to the child.
- Reduce the need and expectations for the child to speak to strangers, adults, or authority figures or to compete with others (such as siblings) to be heard.
- Listen attentively to the child with patience and without showing concern.
- Seek professional guidance if speech is not noticeably more fluent in 2 to 3 months.

109. Which infants with "tongue tie" should have surgical correction?

"Tongue tie," complete or partial ankyloglossia, is the restriction of mobility of the tongue due to a short or thickened lingual frenulum (Fig. 2.9). Complete ankyloglossia, with the tongue unable to protrude past the alveolar ridge or to move laterally, is uncommon but, when present, requires frenuloplasty. Partial ankyloglossia with variability in lingual range of motion occurs in up to 5% of newborns. There is a wide range of opinion regarding the need for "clipping." Partial ankyloglossia can interfere with breastfeeding when there is limited lingual extension or inability to touch the hard palate with the mouth wide open. Ankyloglossia is less commonly associated with speech problems.

Walsh J, Tunkel D. Diagnosis and treatment of ankyloglossia in newborns and infants: a review. *JAMA Otolaryngol Head Neck Surg.* 2017;143(10):1032–1039.

Francis DO, Krishnaswami S, McPheeters M. Treatment of ankyloglossia and breastfeeding outcomes: a systematic review. *Pediatrics.* 2015;135(6):e1459–1466.

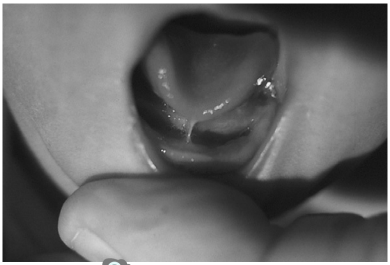

Fig. 2.9 Newborn with ankyloglossia. (From Clark DA. [illegible]f *Neonatology.* Philadelphia, PA: W. B. Saunders; 2000:146.)

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PSYCHIATRIC DISORDERS

110. What are the "11 action signs" for mental health issues in children?

Developed as a screening tool by a number of national experts in pediatric mental health, these are 11 items designed to identify early issues in children and adolescents. If any one of these signs is present, significant impairment is highly possible and expert evaluation is warranted (Table 2.8).

Table 2.8 Action Signs Suggestive of Significant Mental Health Problems

POTENTIAL DISORDER	SIGN
Severe depression	Feeling very sad or withdrawn for more than 2 weeks
Suicidal ideation	Seriously trying to harm or kill yourself or making plans to do so
Panic attack	Sudden overwhelming fear for no reason, sometimes with a racing heart or fast breathing
Severe aggression	Involved in multiple fights, using a weapon, or wanting badly to hurt others
Poor impulse control	Severe out-of-control behavior that can hurt yourself or others
Eating disorder	Not eating, throwing up, or using laxatives to make yourself lose weight
Anxiety	Intense worries or fears that get in the way of your daily activity
Severe inattention/ hyperactivity	Extreme difficulty in concentrating or staying still that puts you in physical danger or causes school failure
Substance abuse	Repeated use of drugs or alcohol
Mood swings	Severe mood swings that cause problems in relationships
Personality changes	Drastic changes in your behavior or personality

Adapted from Jensen PS, Goldman E, Offord E, et al. Overlooked and underserved: "action signs" for identifying children with unmet mental health needs. *Pediatrics.* 2011;128(5):970-979.

111. If a parent has an affective disorder, what is the likelihood that an offspring will have similar problems?

Approximately 20% to 25% of offspring will develop a major affective disorder, which are mood disorders, including depression, bipolar disorder, and anxiety disorder.

112. How does mania differ in children and adolescents?

Mania, a condition of abnormally heightened mood and reduced need for sleep, occurs in about 0.5% to 1% of adolescents and occurs less frequently in prepubertal children. *Younger children* may present with extreme irritability, emotional lability, and aggression. Dysphoria, hypomania, and agitation may be intermixed. Hyperactivity, distractibility, and pressured speech often occur in all age groups. Symptoms in *adolescents* more closely resemble those seen in adults. They include elated mood, flight of ideas, sleeplessness, bizarre behavior, delusions of grandeur, paranoia, and euphoria.

113. What ritualistic behaviors are common in children with obsessive-compulsive disorder (OCD)?

The most common rituals involve **excessive cleaning**, **repeating gross motor rituals** (e.g., going up and down stairs), and **repetitive checking behaviors** (e.g., checking that doors are locked or that homework is correct). Obsessions most commonly deal with fear of contamination. Symptoms tend to wax and wane in severity, and the specific obsessions or compulsions change over time. Most children attempt to disguise their rituals. Anxiety and distress that interfere with school or family life can occur when children fail in their efforts to resist the thoughts or activities. Cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) medications (e.g., sertraline), particularly in combination, can be beneficial.

Krebs G, Heyman I. Obsessive-compulsive disorder in children and adolescents. *Arch Dis Child.* 2015;100(5):495–499.

Gilbert AR, Maalouf FT. Pediatric obsessive-compulsive disorder: management priorities in primary care. *Curr Opin Pediatr.* 2008;20(5):544–550.

114. What are the differences between childhood-onset OCD and adult-onset OCD?

Compared with adult-onset OCD, a patient with childhood-onset OCD is more likely to:

- Have an associated tic disorder
- Have an associated disruptive behavior disorder (e.g., ADHD)
- Have a first-degree relative with OCD (i.e., increased inheritability in childhood onset)
- Be male (adult-onset OCD has female:male predominance)
- Have a better prognosis (nearly half of patients with childhood-onset OCD have subclinical levels of symptom severity, which are signs of remission, by early adulthood; only 20% of untreated adults have remission)

Grant JE. Obsessive-compulsive disorder. *N Engl J Med.* 2014;371(7):1324–1331.
Sarvet B. Childhood obsessive-compulsive disorder. *Pediatr Rev.* 2013;34(1):20.

115. What distinguishes a conduct disorder from an oppositional defiant disorder?

Both are disruptive behavior disorders of childhood and early adolescence. *Conduct disorder* is the more serious disorder in that it is diagnosed when the child's behaviors violate the rights of others (e.g., assault) or are in conflict with major societal norms (e.g., stealing, truancy, setting fires). Children with conduct disorder are at risk for developing the antisocial personality disorder seen in adults. *Oppositional defiant disorder* is characterized by recurrent negative and defiant behaviors toward authority figures.

116. What are common symptoms of depression in children and adolescents?

- Sadness
- School problems
- Tearfulness
- Somatic complaints
- Irritability
- Suicidal ideation
- Negative self-imagery
- Changes in appetite
- Lack of concentration
- Unintended weight changes
- Decreased interest in usual activities
- Sleep problems, including hypersomnia
- Fatigue
- Delusions

117. When should screening for depression be universally initiated?

AAP guidelines recommend universal adolescent screening at ages 12 years and older using one of a number of validated brief depression-specific or longer psychosocial screening tools. Previous studies have shown only 50% of adolescents with depression are diagnosed before adulthood.

Zuckerbrot RA, Cheung A, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): part I. Practice preparation, identification, assessment, and initial management. *Pediatrics.* 2018;141(3):e20174081.

118. How is major depressive disorder in children formally diagnosed?

The DSM-5 criteria require the presence of five or more symptoms (out of nine possible) from the categories of sleep, interest, guilt, concentration, appetite, psychomotor, and suicide during the same 2-week period. A variety of ratings scales (e.g., the Hamilton Depression Rating Scale, the Childhood Depression Inventory, the Child Behavioral Checklist, the Beck Depression Inventory) are available to assist with evaluation.

119. What are treatments for major depressive disorder in children and adolescents?

- **Psychotherapy:** Various types of therapy may be used, including CBT, interpersonal therapy, and family therapy.
- **Pharmacotherapy:** SSRIs have been recommended by the AAP as the treatment of choice for children who warrant pharmacotherapy. There have been controversial warnings by regulatory agencies in Britain and the United States that antidepressant medications may be associated with an increased risk for suicide.

Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): part II. Treatment and ongoing management. *Pediatrics.* 2018;141(3):e20174082.

120. What is the most common childhood-onset psychiatric disorder?

Anxiety disorders, including generalized anxiety disorder, social anxiety disorder, panic disorder, separation anxiety disorder, and agoraphobia. Survey data indicate a lifetime prevalence of any anxiety disorder among U.S. adolescents at a remarkably high 32%, with 8% having severe impairment per DSM-5 criteria. Worldwide, anxiety disorders are also the most common mental disorder in children and adolescents.

National Institute of Mental Health. www.nimh.nih.gov. Accessed July 26, 2019.

Polanczyk GV, Salum GA, Sugaya LA, et al. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry.* 2015;56(3):345–365.

121. What are types of anxiety disorders in children?

- **Separation anxiety disorder:** Developmentally inappropriate, unrealistic, persistent fears of separation from caregivers that interfere with daily activities
- **Panic disorder:** Recurrent, discrete periods of intense fear or discomfort; rare in prepubertal children; may occur with or without agoraphobia (fear or distress in or about places that may limit egress, such as a restaurant)
- **Social anxiety disorder:** Extreme anxiety about social interactions with peers and adults; may manifest as generalized or specific anxiety (e.g., public speaking)

122. Which is preferable for children with anxiety disorders: CBT or medication?

Actually, a **combination of both**. In a study of 488 children using CBT alone, medication (sertraline) alone, combination therapy, or placebo, the combination therapy resulted in 80% “very much” or “much improved” as measured by ratings scales compared with either therapy alone or placebo.

Wehry AM, Beesdo-Baum K, Hennelly MM, et al. Assessment and treatment of anxiety disorders in children and adolescents. *Curr Psychiatry Rep.* 2015;17(7):52.

Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med.* 2008;359(26):2753–2766.

123. What characterizes bipolar disorder?

This is a *mood disorder* with fluctuations of *mania* followed by *depression* and interludes of relatively normal behavior. In children, there are often out-of-control mood swings with dramatic behavior changes, including marked irritability and rage.

- **Manic episode:** Inflated self-esteem, decreased need for sleep, flight of ideas or racing thoughts, distractibility, increase in goal-directed activity, excessive involvement in dangerous activities that have a high potential for dangerous consequences
- **Major depressive episode:** Depressed mood, markedly diminished interest or pleasure in activities, significant changes in weight and appetite, insomnia or hypersomnia, fatigue or loss of energy, diminished ability to concentrate, indecisiveness, recurrent thoughts of death or suicide

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Lee T. Pediatric bipolar disorder. *Pediatr Ann.* 2016;45(10):e362–e366.

Cummings CM, Fristad MA. Pediatric bipolar disorder: recognition in primary care. *Curr Opin Pediatr.* 2008;20(5):560–565.

PSYCHOSOCIAL FAMILY ISSUES

124. How likely is it that children in the United States will experience the separation or divorce of their parents?

About half of first marriages end in divorce. In the United States, about 1.5 million children experience parental divorce each year. It is estimated that nearly 75% of black children and 40% of white children born to married parents will experience their parents’ divorce before they are 18 years old. An addition to this stressor is that 50% of individuals who divorce will remarry within 4 years, thus creating another major family transition for a child. Of stepfamilies, nearly 90% consist of a biologic mother and a stepfather.

Tanner JL. Separation, divorce and remarriage. In Carey WB, Crocker AC, Coleman WL, et al, eds. *Developmental-Behavioral Pediatrics.* 4th ed. Philadelphia, PA: Saunders Elsevier; 2009:126.

125. How do children of different ages vary in their response to parental divorce?

- **Preschool age** *(2 to 5 years)*: May exhibit regression in developmental milestones (e.g., toilet training); irritability; sleep disturbances; preoccupation with fear of abandonment; demanding with remaining parent
- **Early school age** *(6 to 8 years)*: May demonstrate open grieving; preoccupied with fear of rejection and of being replaced; half may have a decrease in school performance

- **Later school age** *(9 to 12 years)*: May exhibit profound anger at one or both parents; more likely to distinguish one parent as the culprit causing the divorce; deterioration in school performance and peer relationships; sense of loneliness and powerlessness
- **Adolescence:** Significant potential for acute depression and even suicidal ideation; acting-out behavior (substance abuse, truancy, sexual activity); self-doubts about own potential for marital success

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Kleinsorge C, Covitz LM. Impact of divorce on children: developmental considerations. *Pediatr Rev.* 2012;33:147–154.
Hetherington EM. Divorce and the adjustment of children. *Pediatr Rev.* 2005;26(5):163–169.

126. What factors are central to a good outcome after a divorce?

- Ability of parents to set aside or resolve conflicts without involving children
- Emotional and physical availability of custodial parent to the child
- Parenting skills of custodial parent
- Extent to which child does not feel rejected by noncustodial parent
- Child's temperament
- Presence of supportive family network
- Absence of continuing anger or depression in the child

Cohen GJ, Weitzman CC. Helping children and families deal with divorce and separation. *Pediatrics.* 2016;138(6):e20163020.

127. What is the "vulnerable child syndrome"?

The *vulnerable child syndrome* is characterized by excessive parental concern about the health and development of their child. It usually occurs after a medical illness in which the parents are understandably upset or worried about the child's health (e.g., prematurity, congenital heart disease). However, this concern persists despite the child's recovery. Problems of the syndrome can include pathologic separation difficulties for parent and child, sleep problems, overprotectiveness, and overindulgence. Children are at risk for behavioral, school, and peer-relationship problems.

Schmitz K. Vulnerable child syndrome. *Pediatr Rev.* 2019;40(6):313–315.

128. How does the cognitive understanding of death evolve?

- **Toddler** *(<2 years)*: Death as separation, abandonment, or change; may become irritable or withdrawn
- **Preschool** *(2 to 6 years)*: Prelogical thought with magical and egocentric beliefs that the child may be responsible for the death; death as temporary and reversible
- **School age** *(6 to 10 years)*: Concrete logical thinking; death as permanent and universal but due to a specific illness or injury rather than as a biologic process; death is something that occurs to others; may develop a morbid interest in death
- **Adolescence** *(>10 years)*: Abstract logical thinking; more complete comprehension of death; death as a possibility for self

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Linebarger JS, Sahler OJ, Egan KA. Coping with death. *Pediatr Rev.* 2009;30(9):350–355.

129. How common is adoption in the United States?

Approximately 2% (or 1.8 million) of U.S. children are adopted. About 38% are adopted from foster care, 38% from private domestic adoption, and 24% from international adoption. About one in four adopted children are adopted by relatives.

Jones VF, Schulte EE, Committee on Early Childhood; Council on Foster Care, Adoption, and Kinship Care. The pediatrician's role in supporting adoptive families. *Pediatrics.* 2012;130(4):e1040–e1049.

130. Should adopted children be informed of their adoption?

Yes. It should not occur as a one-time event, but rather increasing amounts of information can be given over time. Most preschool children will not understand the process or meaning of adoption, and for them, disclosure should be guided by what the child wants to know. School-age children should be aware of their adoption and feel comfortable discussing it with their parents. This helps remove any veil of secrecy, which could carry an implication of adoption as a negative condition.

Jones VF, Schulte EE, Committee on Early Childhood; Council on Foster Care, Adoption, and Kinship Care. The pediatrician's role in supporting adoptive families. *Pediatrics.* 2012;130(4):e1040–e1049.

131. Who are "latchkey" children?

The term refers to the millions of children <18 years of age who are in unsupervised care after school because they are members of families in which one or two parents work. Because of the enormous variability of circumstances, the consequences may be positive (e.g., increased maturity, self-reliance) or negative (e.g., isolation, feelings of neglect). Increased after-school programs may minimize negative consequences.

SCHOOL PROBLEMS

132. How is "learning disability" defined?

Currently, as defined by federal legislation, a specific *learning disability* (LD) "means a disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, which may manifest itself in an imperfect ability to listen, think, speak, read, write, spell, or to do mathematical calculations." Such difficulties are not due to visual, hearing, or motor handicaps; emotional problems; intellectual disability; or environmental, social, cultural, or economic issues. This implies a discrepancy between academic achievement and that expected for age, schooling, and intelligence.

U.S. Department of Education. Individuals with Disabilities Education Act (IDEA). www.ed.gov. Accessed January 18, 2020.

133. What distinguishes dyslexia, dyscalculia, and dysgraphia?

- *Dyslexia* is a reading LD. It is the most common LD, affecting 3% to 15% of school-age children. About 80% of children identified as learning disabled have dyslexia (or a specific reading difficulty) as their primary diagnosis. Characterized by problems decoding single words (i.e., reading single words in isolation), dyslexia is usually the result of deficits in phonological processing.
- *Dyscalculia,* or specific mathematics disability, affects 1% to 6% of children. Mathematics disabilities involve difficulties in computation, math concepts, and/or the application of those concepts to everyday situations.
- *Dysgraphia,* or disorder of written expression, affects up to 10% of children. Difficulties with writing have several possible etiologies, including problems with fine motor control, linguistic abilities, visual-spatial skills, motor planning, proprioception, attention, memory, and sequencing.

Feder KP, Majnemer A. Handwriting development, competency, and intervention. *Dev Med Child Neurol.* 2007;49(4):312–317.
Shaywitz SE, Shaywitz BA. Dyslexia. *Pediatr Rev.* 2003;24(5):147–152.

134. What are clues that a school-age child may have dyslexia?

- **Problems in speaking:** Mispronunciation of multisyllable words; hesitant, choppy speech; imprecise language
- **Problems in reading:** Trouble reading and sounding out unfamiliar words; reading aloud is hesitant and choppy; handwriting is very messy; extremely poor speller; great difficulties in learning a foreign language; often a family history of reading or spelling difficulties

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Shaywitz SE, Gruen JR, Shaywitz BA. Management of dyslexia, its rationale, and underlying neurobiology. *Pediatr Clin North Am.* 2007; 54(3):609–623.

135. How are the two types of school avoidance behaviors distinguished?

- **Anxiety-related avoidance:** Excessive fears (about peers, potential for teasing, grades); often an overprotective parent; typically excellent students with no classroom behavioral issues; girls affected more often than boys; symptoms are often physiologic manifestations of anxiety (e.g., headache, abdominal pain)
- **Secondary-gain avoidance:** No anxiety about school; absence often follows lingering illness; "rewarded" at home for absence (e.g., sympathy, television); often are poor students; boys affected more often than girls; symptoms are fabricated or exaggerated (e.g., sore throat, extremity pain)

Schmitt BD. School avoidance. In Augustyn M, Zuckerman B, Caronna EB, eds. *The Zuckerman Parker Handbook of Developmental and Behavioral Pediatrics for Primary Care.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:309–314.

136. How much of a problem are bullies?

Bullying has been defined as "intentional, unprovoked abuse of power by one or more children to inflict pain or cause distress to another child on repeated occasions." It is a universal problem in schools worldwide. The victims frequently experience a range of psychological, psychosomatic, and behavioral problems that include anxiety, insecurity, low self-esteem, sleeping difficulties, bedwetting, sadness, and frequent bouts of headache and abdominal pain. In this age of social media and social networking, electronic bullying (or cyberbullying) is a rapidly growing problem.

Rettew DC, Pawlowski S. Bullying. *Child Adolesc Psychiatr Clin N Am.* 2016;25(2):235–242.

SLEEP PROBLEMS

137. What is the average daily sleep requirement by age?

- **Newborns**: 16 to 20 hours
- **6 months**: 13 to 14 hours
- **Toddlers** *(1 to 3 years)*: 12 hours
- **Preschoolers** *(3 to 6 years)*: 11 to 12 hours
- **Middle childhood** *(6 to 12 years)*: 10 to 11 hours
- **Adolescents** *(>12 years)*: 9 hours

Chamness JA. Taking a pediatric sleep history. *Pediatr Ann.* 2008;37(7):503.

138. When do infants begin to sleep through the night?

By the time they are about 3 months old, about 70% of infants (slightly more for bottle-fed babies and slightly less for breastfed babies) will not cry or awaken their parents between midnight and 6 AM. By 6 months, 90% of infants fit into this category, but between 6 and 9 months, the percentage of infants with night awakenings increases.

139. What is the Ferber method that may allow parents to sleep more soundly?

In addition to setting bedtime routines and eliminating nighttime feedings (typically by 6 months) as promoters of longer sleep, the *Ferber method* is one approach of systematic ignoring (also called "extinction") that facilitates sleeping through the night. In the Ferber method (named after a Boston Children's Hospital sleep expert), a parent leaves the room after placing down an awake infant but returns at intervals to check on and to reassure the infant. Other approaches include unmodified extinction, also known as "cry it out," in which a parent leaves the room and does not return to check on the infant. A third method allows the parent to remain in the room, either providing support by patting or picking up the child or, in the fourth method, providing no additional support. The Ferber method, the "cry it out" method, and the continuous parent without support method have similar success rates of 80% by 2 weeks.

Honaker SM, Schwichtenberg AJ, Kreps TA, et al. Real-world implementation of infant behavioral sleep interventions: results of a parental survey. *J Pediatr.* 2018;199:106–111.e2.

140. How common are sleep problems in elementary school-age children?

About 40% of children between 7 and 12 years old experience sleep-onset delay, 10% experience night awakening, and 10% have significant daytime sleepiness. Some studies have shown that the extent of sleep is also inversely related to teacher-reported psychiatric symptoms.

Chamness JA. Taking a pediatric sleep history. *Pediatr Ann.* 2008;37(7):503.

141. What are parasomnias?

Parasomnias are undesirable physical phenomena that occur during sleep. Examples include night terrors, nightmares, sleepwalking, nocturnal enuresis, sleep bruxism, somniloquy (sleep talking), and body rocking. Between the ages of 3 and 13 years, nearly 80% of all children will have had at least one parasomnia.

142. At what age do sleepwalking and sleep talking occur?

Sleepwalking occurs most commonly between the ages of 5 and 10 years. As many as 15% of children between the ages of 5 and 12 years may have somnambulated once, and as many as 10% of 3- to 10-year-old children may sleepwalk regularly. The sleepwalking child is clumsy, restless, and walking without purpose, and the episode is not remembered. Injury is common during this outing. *Sleep talking* (somniloquy) is monosyllabic and often incomprehensible. Both conditions usually end before the age of 15 years. Severe cases may benefit from diazepam or imipramine therapy.

143. What is the difference between nightmares and night terrors?

- *Nightmares* are frightening dreams that occur during rapid eye movement (REM) sleep (usually during the last half of the night) and that may be readily recalled on awakening. The child is aroused without difficulty and is usually easily consolable, but returning to sleep after a nightmare may be problematic.

- *Night terrors* are brief episodes that occur during non-REM stage IV sleep. They usually last 30 seconds to 5 minutes, during which a child sits up, screams, and appears aroused, often staring and sweating profusely. The child cannot be consoled, rapidly goes back to sleep, and does not recall the episode in the morning. The onset of night terrors in an older child or persistent multiple attacks may indicate more serious psychopathology.

144. What recommendation should be given to a parent whose child is having night terrors?

An explanation of the phenomenon to the parent, with emphasis on the fact that the child is still asleep during the episode and should not be awakened, is all that is needed. If stress or sleep deprivation coincides with the night terrors, these factors should be addressed. If this is not successful, other approaches may be considered.

- When night terrors occur at the same time each night, the parent may awaken the child 15 minutes before the anticipated event over a 7-day period and keep him or her awake for at least 5 minutes. This often disrupts the sleep cycle and results in resolution of the problem.
- If night terrors remain problematic, a short course of a benzodiazepine at bedtime may result in cessation of the night terrors, presumably via some resetting of the sleep cycle.

145. What is the association between periodic limb movement disorders (PLMDs) and iron deficiency?

PLMDs are repetitive, highly stereotyped limb movements that occur multiple times during sleep, cause disturbances in sleep, and are not explained by another medical condition. Diagnosis is typically made by polysomnography. PLMDs are closely related to restless legs syndrome (RLS), a different diagnosis that involves nonsleep urgency to move the legs, with this urgency worsening during rest. There can be some overlap between the two diagnoses. Both conditions are associated with iron deficiency. Measurement of iron stores (most typically with a ferritin level) is indicated. Oral iron supplementation is recommended if there is evidence of iron deficiency. The mechanism by which iron deficiency may contribute to these problems remains unclear.

Munzer T, Felt B. The role of iron in pediatric restless legs syndrome and periodic limb movements in sleep. *Semin Neurol.* 2017; 37(4):439–445.

VISUAL DEVELOPMENT AND DISORDERS

146. How well does a newborn see?

Because of the short diameter of the eye, as well as retinal immaturity, a newborn's visual acuity is roughly 20/200 to 20/400. The human face is the most preferred object of fixation during early infancy. The light sense is one of the most primitive of all visual functions and is present by the seventh fetal month.

147. Do babies make tears?

Alacrima, or the absence of tear secretion, is not uncommon during the newborn period, although some infants may produce reflexive tearing at birth. In most others, tearing is delayed and typically not seen until the infant is 2 to 4 months old. Persistent lack of tearing is seen in Riley-Day syndrome (familial dysautonomia). This is a rare genetic syndrome seen in the Ashkenazi Jewish population, affecting 1 in 10,000 newborns. Other symptoms include diaphoresis, skin blotching or marbling, hyporeflexia, and indifference to pain.

148. At what age does an infant's eye color assume its permanent color?

A neonate's eyes will never be lighter than they are at birth. The pigmentation of the iris in all races increases over the first 6 to 12 months. The eye color is usually defined by 6 months and always by 1 year.

149. A 2-week-old infant with intermittent eye discharge and clear conjunctiva has what likely diagnosis?

Nasolacrimal duct obstruction, seen in roughly 5% of newborns, is typically due to an intermittent blockage at the lower end of the duct. Massaging the area and watchful waiting are generally all that is needed. Almost all cases (95%) resolve by 6 months, and a few resolve thereafter. Occasionally, *acute dacryocystitis* can develop with pain, erythema, and edema in the lacrimal sac region, which, depending on the severity and age of the patient, may warrant intravenous (IV) antibiotics (Fig. 2.10). Ophthalmologic referral during the first 6 months is usually unnecessary, unless there are multiple episodes of dacryocystitis or a large congenital mucocele. Most ophthalmologists advise referral between 6 and 13 months because during this period, simple probing of the duct is curative in 95% of patients. After 13 months, the cure rate by probing alone falls to 75%, and silicone intubation of the duct is often necessary.

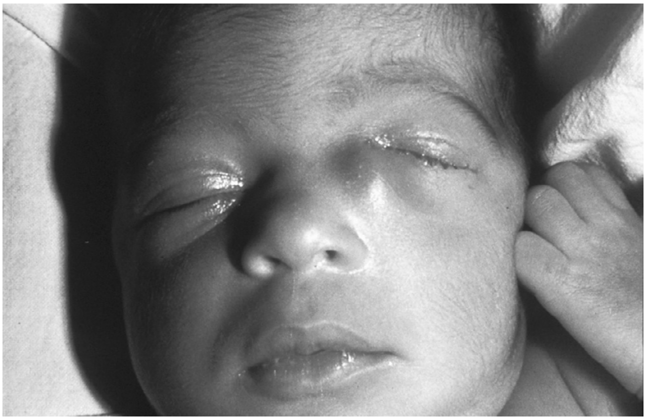

Fig. 2.10 Congenital nasolacrimal duct obstruction with infected dacryocele (dacryocystitis) with swelling and erythema along the left side of the nose. (From Bergelson JM, Shah SS, Zaoutis TE. *Pediatric Infectious Diseases: The Requisites in Pediatrics.* Philadelphia, PA: Elsevier Mosby; 2008:76.)

150. What are the valves of Rosenmüller and Hasner?

These are narrowings of the nasolacrimal drainage system where blockage can commonly occur in infancy. This is particularly true at the Hasner valve due to persistence of an embryonic membrane (Fig. 2.11).

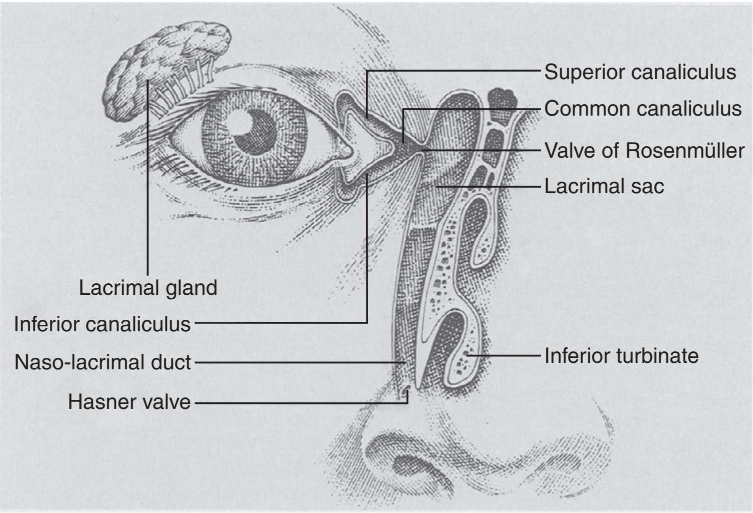
Superior canaliculus
Common canaliculus
Valve of Rosenmüller
Lacrimal sac
Lacrimal gland
Inferior canaliculus
Naso-lacrimal duct
Inferior turbinate
Hasner valve

Fig. 2.11 The nasolacrimal drainage system. (From Ogawa GSH, Gonnering RS. Congenital nasolacrimal duct obstruction. *J Pediatr.* 1991;119:13.)

151. What is normal visual acuity for children?

- *Birth to 6 months:* Gradually improves from 20/400 to 20/80
- *6 months to 3 years:* Improves from 20/80 to 20/50
- *2 to 5 years:* Improves to 20/40 or better, with a less than two-line difference between left and right eyes on visual charts
- *>5 years:* 20/30 or better, with a less than two-line difference between eyes on visual charts

It should be noted that almost 20% of children require eyeglasses for correction of refractive errors before adulthood.

152. When do binocular fixation and depth perception develop in children?

Binocularity of vision depends primarily on the adequate coordination of the extraocular muscles and is normally established by 3 to 6 months of age. At about 6 to 8 months, early evidence of depth perception is seen, but it is still poorly developed. Depth perception becomes very accurate at 6 or 7 years and continues to improve through the early teenage years.

153. How does refractive capacity vary with age?

The newborn infant is typically slightly hyperopic (farsighted). The mild hyperopia actually increases slowly for about the first 8 years. It then decreases gradually until adolescence, when vision is emmetropic (no refractive error). After 20 years, there is a tendency for myopia (nearsightedness).

154. How are the degrees of blindness classified?

The World Health Organization defines blindness as follows:

- **Visual impairment:** Snellen visual acuity of $\leq$20/60 (best eye corrected)
- **Social blindness:** Snellen visual acuity of $\leq$20/200 or a visual field of $\leq$20 degrees
- **Virtual blindness:** Snellen visual acuity of $<$20/1200 or a visual field of $\leq$10 degrees
- **Total blindness:** No light perception

American Foundation for the Blind. www.afb.org. Accessed January 18, 2020.
Prevent Blindness America. www.preventblindness.org. Accessed January 18, 2020.

155. What is strabismus?

Strabismus is the misalignment of the eyes with either an in-turning (esotropia), out-turning (exotropia), or up-turning (hypertropia) of one eye.

156. A 2-month-old baby is noted to have eyes that appear to turn outward rather than looking forward. Is this strabismus?

Yes, but intervention is not needed unless the symptom persists beyond 2 to 3 months of age. Infants do not focus well because the macula and fovea are poorly developed at birth. Therefore it is not uncommon for infants to occasionally have an inward crossing of the eyes or for their eyes to be turned slightly outward to 10 or 15 degrees. Strabismus is defined as any deviation from perfect ocular alignment. However, most newborns (up to 70%) will be found to have an exodeviated alignment (i.e., looking somewhat out) rather than an orthotropic (i.e., straight) alignment. Most infants will become orthotropic by the time they are 4 months old.

Persistent in-turning of the eyes for more than a few seconds or outward deviation of more than 10 to 15 degrees requires ophthalmologic referral.

157. What are the types of childhood strabismus?

- **Strabismus of visual deprivation** occurs when normal vision in one or both eyes is disrupted by any cause. The most serious varieties occur with tumors (e.g., retinoblastoma). In children with ocular tumors, strabismus may be the presenting sign.
- **Infantile** or **congenital esotropia** occurs within the first few months of life, usually as an isolated condition and often with large-angle strabismus. Corrective surgery is usually required.
- **Accommodative esotropia** commonly occurs between the ages of 3 months and 5 years in very farsighted (hyperopic) children. These children use extra lens accommodation because of their visual problems, which leads to persistent convergence. Eyeglasses to correct the hyperopia often correct the esotropia.
- **Intermittent exotropia** appears between the ages of 2 and 8 years as misalignment that is often brought on by fatigue, visual inattention, or bright sunlight. There is a strong hereditary component. Surgery is often necessary after the correction of refractive errors and the elimination of any pathology that might have caused visual deprivation.
- **Incomitant strabismus** is caused by limited eye movement due to restriction (e.g., periocular scarring) or muscle paresis, most commonly from neurologic (e.g., cranial nerve palsies) or muscle pathology. The size of the deviation changes depending on the gaze because of the restrictions of eye movement.

Wright KW. *Pediatric Ophthalmology for Primary Care.* 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008:49–70.

158. What separates pseudostrabismus from true strabismus?

Often a cause of unnecessary ophthalmologic referrals, *pseudostrabismus* is the appearance of ocular misalignment (usually esotropia) that occurs in children with a broad and flat nasal bridge and prominent epicanthal folds. The iris appears to be shifted to the midline, with differing amounts of white sclera on each side (Fig. 2.12). This is a common condition that may occur in up to 30% of newborns and is more common in Asian children. No treatment is required. It may be distinguished from true esotropia (or strabismus) by the observation of full extraocular movements, by symmetric reflections of a flashlight on the cornea from a distance of about 12 inches (although this test as a measure of strabismus is more accurate in infants $\geq$6 months old), and by normal visualization of red reflexes by direct ophthalmoscopy.

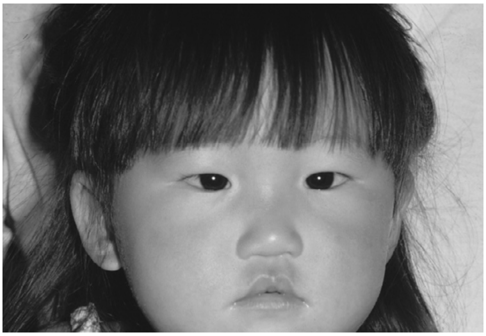

Fig. 2.12 Pseudoesotropia. Note that the wide nasal bridge and prominent epicanthal folds create the illusion of an esotropia. The corneal light reflexes are centered in each eye; therefore the eyes are straight. (From Gault JA. *Ophthalmology Pearls.* Philadelphia, PA: Hanley & Belfus; 2003:45.)

159. What is amblyopia?

Amblyopia refers to decreased visual acuity in one eye that is not correctable by glasses and is a result of decreased visual stimulation of that eye. The visual cortex adheres to the concept of "use it or lose it." Amblyopia is the most common cause of vision loss in children younger than 6 years, and it occurs in 1% to 2% of this age group and in 2% to 2.5% of the general population.

160. What are the causes of amblyopia?

- **Strabismus:** Input from one eye is suppressed to avoid double vision.
- **Anisometropic amblyopia:** Significant refraction differences cause the suppression of images from the weaker eye.
- **Deprivation:** Images received are unclear (e.g., from congenital cataracts or ptosis).
- **Occlusion amblyopia:** This is typically iatrogenic. Prolonged covering of the preferred eye as a treatment for amblyopia can cause changes in visual acuity in the preferred eye.

Mittelman D. Amblyopia. *Pediatr Clin North Am.* 2003;50(1):189–196.

161. Which treatments are effective for amblyopia?

The first step involves providing a clear retinal image with use of eyeglasses or contact lenses for refractive errors and with removal of any obstructing opacities such as cataracts. Occlusion of the good eye allows stimulation of the visual cortex correlating to the amblyopic eye. Traditionally, prolonged patching has been the therapeutic mainstay. By causing papillary dilation and paralysis of accommodation, 1% atropine drops in the better eye cause blurring and reliance on the amblyopic eye, particularly for patients who are hyperopic. Recent studies have shown that both atropine and patching are effective treatments for patients from 3 to 12 years and that shorter durations of patching are as effective as longer periods.

Tailor V, Bossi M, Greenwood JA, Dahlmann-Noor A. Childhood amblyopia: current management and new trends. *Br Med Bull.* 2016;119(1):75–86.

Repka MX, Kraker RT, Holmes JM, et al. Atropine vs. patching for treatment of moderate amblyopia. *JAMA Ophthalmol.* 2014;132(7):799–805.

162. What is the red reflex test?

An essential component of any eye examination in an infant or child, the *red reflex test* is an evaluation of reflected light off the ocular fundus. A direct ophthalmoscope, set to a lens power of "0," is projected onto both eyes from a distance of 18 inches. A red image, symmetric from both eyes, should be visible. Abnormal color (particularly white), incomplete coloring (dark spots present), or asymmetric coloring warrant ophthalmologic consultation because these can represent cataracts, glaucoma, retinoblastoma, strabismus, or high refractive errors.

Anderson J. Don't miss this! Red flags in the pediatric eye examination: abnormal red reflex. *J Binocul Vis Ocul Motil.* 2019;69(3):106–109.

American Academy of Pediatrics, Section on Ophthalmology. Red reflex examination in neonates, infants, and children. *Pediatrics.* 2008;122(6):1401–1404.

163. Why are early diagnosis and treatment critical for patients with congenital cataracts?

Delay in treatment can lead to irreversible vision loss as a result of deprivation amblyopia. Cataracts undiagnosed for as little as 4 to 8 weeks after birth can result in permanent deficits. In general, the younger the child, the more urgent the need for evaluation if cataracts are suspected.

164. What is ectopia lentis?

Ectopia lentis refers to the displacement or dislocation of the lens. It may be due to trauma, but it has also been associated with systemic diseases such as Marfan syndrome, homocystinuria, and congenital syphilis.

165. What diseases may present with a white pupil?

Leukocoria, or white pupil, may be a result of any intraocular abnormality behind the pupillary space whereby light is obstructed (Fig. 2.13). This includes infants with cataracts, retinoblastoma, or retinopathy of prematurity who develop retinal detachment.

Varughese R. Fifteen minute consultation: a structured approach to the child with a white red reflex. *Arch Dis Child Educ Pract Ed.* 2014; 99(5):162–165.

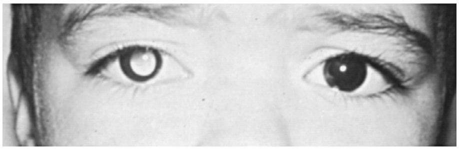

Fig. 2.13 Leukocoria. White papillary reflex in a child with retinoblastoma. (From Kleigman RM, Stanton BF, Schor NF, et al. *Nelson Textbook of Pediatrics.* 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:2157.)

166. How common are unequally sized pupils?

Up to 20% of the normal population can have physiologic **anisocoria** (inequality of pupil size) of up to 0.5 mm. The percentage of difference remains the same in bright or dim lighting.

167. Is heterochromia normal?

Yes, if it is an *isolated* finding. Heterochromia irides, or difference in iris colors, can be a familial autosomal dominant trait. It is also seen in some syndromes (e.g., Waardenburg, Horner). However, changes in color can occur from trauma, hemorrhage, inflammation (uveitis, iridocyclitis), malignancy (retinoblastoma, neuroblastoma), or glaucoma, or after intraocular surgery.

KEY POINTS: VISUAL DEVELOPMENT AND DISORDERS

1. Red reflex testing should be done routinely for all infants.
2. Suspected cataracts require urgent evaluation, particularly in newborns and younger infants.
3. Uncorrected visual acuity errors in children <8 years old can cause irreversible, lifelong problems.
4. Amblyopia accompanies strabismus in 30% to 60% of cases.
5. Pseudoesotropia, a normal variant, mimics strabismus as a result of widened epicanthal folds. Unlike strabismus, corneal light reflections are equal.
6. Nasolacrimal duct obstruction is common in infants and resolves spontaneously in >95% of cases by 6 months of age.

168. When are children aware of color differences?

By 6 months of age, infants have perceptual awareness of colors. By age 2.5 years, 50% of children can match cubes or cards by color. By 3.5 to 4 years, 50% can name four colors correctly.

Sharma A. Developmental examination: birth to 5 years. *Arch Dis Child Educ Pract Ed.* 2011;96(5):162–175.

169. How is color blindness inherited?

Color blindness typically involves the variable loss of the ability to distinguish colors, especially red, green, and blue. The defects can be partial (anomaly) or complete (anopia). Defects in appreciating *red or green* color are transmitted in an **X-linked recessive** manner and affect up to 1% and 6%, respectively, of the male population. *Blue* color blindness is an **autosomal dominant** phenomenon and occurs in 0.1% of the population.

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CHAPTER 3

PEDIATRIC CARDIOLOGY

Thomas J. Starc, MD, MPH, Constance J. Hayes, MD and Allan J. Hordof, MD

CLINICAL ISSUES

1. Is cardiac disease the most common cause of chest pain in children?

A cardiac cause of chest pain is **very uncommon** and represents less than 1% of cases in a published series. The most common identifiable causes involve *musculoskeletal* pain (e.g., strained intercostal muscles, costochondritis, Tietze syndrome, precordial catch syndrome), which occurs in one-quarter to one-half of cases. Other causes are *pulmonary* disease (e.g., asthma, cough illness, pneumonia, pleurisy), *gastrointestinal* disease (e.g., reflux, esophagitis, gastroenteritis), and miscellaneous diseases (e.g., sickle cell crisis, herpes zoster). Other possibilities include *psychogenic* (e.g., anxiety, hyperventilation/disordered breathing) and the always present *idiopathic* diseases (which may represent the largest category).

Collins SA, Griksaitis MJ, Legg JP. 15-minute consultation: a structured approach to the assessment of chest pain in a child. *Arch Dis Child Educ Pract Ed.* 2014;99(4):122–126.

2. What is the clinical distinction between costochondritis and Tietze syndrome?

- *Costochondritis* involves sharp, anterior chest wall pain that emanates from *multiple* costochondral and costosternal junctions. Causes can be inflammatory, posttraumatic, or, less commonly, infectious (including bacterial or fungal). Because the costal cartilage is avascular, it is susceptible to infection after surgery or trauma. This can be delayed and insidious in presentation. Palpation and percussion over the affected areas typically reproduce the pain. Swelling is not a prominent feature.
- *Tietze syndrome* is a localized form of costochondritis, usually involving just one costochondral junction (typically the second or third costochondral junction). A tender, swollen (but not hot) 1- to 4-cm mass is frequently palpable at the site. Onset is more commonly related to trauma.

3. What are potential red flags that increase the likelihood of a cardiac cause for chest pain?

- Personal history of acquired or congenital cardiac disease
- Exertional syncope
- Exertional “cardiac-type” chest pain (e.g., centrally located with radiation to left arm/jaw, crushing pain or heaviness)
- Hypercoagulable or hypercholesterolemic state
- Family history of sudden death <35 years, young-onset ischemic heart disease, inherited arrhythmias (such as long QT syndrome)
- Connective tissue disorders
- History of cocaine/amphetamine use

Collins SA, Griksaitis MJ, Legg JP. 15-minute consultation: a structured approach to the assessment of chest pain in a child. *Arch Dis Child Educ Pract Ed.* 2014;99(4):123.

4. A child is brought to your office with a history of sharp, stabbing, localized chest pain that occurs at rest and resolves completely after 1 minute. There are no associated symptoms. What is the likely diagnosis?

Precordial catch syndrome, also called *Texidor twinge* after the original 1955 describer, may be an underappreciated phenomenon in children with characteristic features that often prompt extensive and unproductive diagnostic workups. It manifests as sudden-onset chest pain in children, very localized (patient points to area with one or two fingers), which occurs most commonly over the left sternal border, right anterior chest, or flanks with variation of site from episode to episode. The pain occurs typically at rest without provocation, is exacerbated by deep breaths (so the patient breathes very shallowly), and usually lasts 30 seconds to 3 minutes. Unlike cardiac, pulmonary, gastrointestinal, or chest wall causes, there is a paucity of associated symptoms (e.g., no palpitations, pallor, flushing, fever, tenderness, or near-syncope). Physical examination, when done during the episode, is normal. The cause is unknown. Pain may originate from the parietal pleura or chest wall (e.g., rib or cartilage), but is not cardiac or pericardial in origin. Ancillary testing, when done, is normal. Management is expectant with reassurance.

Gumbiner CH. Precordial catch syndrome. *South Med J.* 2003;96(1):38–41.

5. What is the significance of mitral valve prolapse (MVP)?

MVP occurs when one or both mitral valve leaflets billow excessively into the left atrium near the end of systole. Some studies show that up to 13% of normal children have some degree of posterior leaflet prolapse on echocardiography. There is a spectrum of anatomic abnormalities, the most minor of which are variations of normal. Children with clinical features of mitral valve insufficiency constitute the pathologic category. Whenever auscultation reveals the classic findings of MVP, referral to a pediatric cardiologist is recommended. This allows for evaluation of the child for possible accompanying cardiac abnormalities (e.g., mitral insufficiency, secundum atrial septal defects [ASDs]) and confirmation of the diagnosis.

6. What connective tissue diseases may be associated with MVP?

- Marfan syndrome
- Ehlers-Danlos syndrome
- Pseudoxanthoma elasticum
- Osteogenesis imperfecta
- Hurler syndrome

7. What are the common types of vascular rings and slings?

Vascular rings occur when the trachea and/or the esophagus is encircled by aberrant vascular structures. *Vascular slings* are compressions that are caused by nonencircling aberrant vessels (Table 3.1).

Table 3.1 Vascular Rings and Slings

	FREQUENCY (%)	SYMPTOMS	TREATMENT
“Complete” Rings			
Double aortic arch	50	Respiratory difficulty, worsened by feeding or exertion (onset <3 mo)	Surgical division of a smaller arch (usually the left)
Right aortic arch with left ligamentum arteriosum	45	Mild respiratory difficulty (onset later in infancy); swallowing dysfunction	Surgical division of ligamentum arteriosum
“Incomplete” Rings			
Anomalous innominate artery	<5	Stridor and/or cough in infancy	Conservative management or surgical suturing of artery to the sternum
Aberrant right subclavian artery	<5	Occasional swallowing dysfunction	Usually no treatment necessary
Vascular sling or anomalous left pulmonary artery	Rare	Wheezing and cyanotic episodes during first weeks of life	Surgical division of anomalous left pulmonary artery and anastomosis to the main pulmonary artery; may also need tracheal reconstruction

Adapted from Park MK. *Pediatric Cardiology for Practitioners.* 5th ed. St. Louis, MO: Mosby Elsevier; 2008:578.

8. What evaluations are commonly done if a vascular ring is suspected?

- **Chest radiograph:** For detection of possible right-sided aortic arch
- **Barium esophagram:** Previously considered the gold standard for diagnosis (before magnetic resonance imaging [MRI]); confirms external indentation of esophagus in up to 95% of cases (Fig. 3.1)
- **MRI:** Noninvasive and now used as the primary diagnostic modality
- **Arteriogram:** Precise delineation of vascular anatomy; rarely needed because of MRI
- **Echocardiogram:** Should not be relied on for identifying the ring itself, but important when evaluating for other congenital heart lesions that can occur in patients with vascular rings

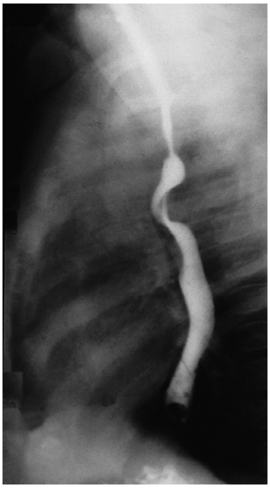

Fig. 3.1 Barium swallow in a toddler with posterior compression of the esophagus and trachea from a vascular ring. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis*. 4th ed. St. Louis, MO: Mosby; 2002:540.)

9. How are cardiomyopathies classified in children?

- **Dilated cardiomyopathy** is the most common variety. Etiology is usually unknown. Anatomically, the heart is normal, but both ventricles are dilated. Older children exhibit symptoms of congestive heart failure (CHF). Infants demonstrate poor weight gain, feeding difficulty, and respiratory distress. In all pediatric age groups, a more acute presenting symptom can be shock.
- **Hypertrophic cardiomyopathy with left ventricular (LV) outflow obstruction** is also known as *idiopathic hypertrophic subaortic stenosis* and *asymmetric septal hypertrophy.* Of patients with this condition, most have some degree of LV outflow tract obstruction as a result of abnormal hypertrophy of the subaortic region of the intraventricular septum. Most of these defects are inherited in an autosomal dominant fashion.
- **Hypertrophic cardiomyopathy without LV outflow obstruction** is also usually of unknown etiology. It may be associated with systemic metabolic disease, particularly a storage disease. Cardiomegaly is a constant feature.
- **Restrictive cardiomyopathy** is associated with abnormal diastolic function of the ventricles. The ventricles may be of normal size, or they may be hypertrophied with normal systolic function. The atria are typically enlarged. The etiology is usually unknown, but restrictive cardiomyopathy may be seen with storage diseases.

Ware SM. Evaluation of genetic causes of cardiomyopathy in childhood. *Cardiol Young.* 2015;25(Suppl 2):43-50.

Pettersen MD. Cardiomyopathies encountered commonly in the teenage years and their presentation. *Pediatr Clin North Am.* 2014;61(1):173–186.

10. What mineral is added to hyperalimentation fluids to prevent a potential cardiomyopathy?

Selenium is routinely added to hyperalimentation fluids to prevent selenium deficiency, which can be a cause of both skeletal muscle weakness and cardiomyopathy. This “acquired” heart disease has been described in patients on long-term hyperalimentation (before modern hyperalimentation); patients with acquired immunodeficiency syndrome (AIDS), chronic diarrhea, and wasting disease. It has also been described in children living in the Keshan County in northeast China, where the soil is naturally low in selenium. It is typically reversible with the addition of selenium to the diet or intravenous fluids.

11. What are the cardiac causes of sudden cardiac death in children and adolescents?

Sudden death occurs because of ventricular fibrillation in the setting of myocardial or coronary abnormalities or underlying primary rhythm disorders. The main structural causes are hypertrophic cardiomyopathy (particularly with extreme LV hypertrophy), anomalies of the coronary artery (congenital or acquired), Marfan syndrome, and arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy. Electrocardiogram (ECG) abnormalities that can lead to sudden death include Wolff-Parkinson-White (WPW) syndrome, prolonged QT syndrome, atrioventricular (AV) block, and Brugada syndrome (a genetic syndrome where the electrical activity of the heart is abnormal). Children with congenital heart disease (CHD) (e.g., severe aortic stenosis, Ebstein anomaly) are at higher risk for sudden death.

Scheller RL, Johnson L, Lorts A, Ryan TD. Sudden cardiac arrest in pediatrics. *Pediatr Emerg Care.* 2016;32(9):630–636.

12. What historical features may identify the patient who is at risk for sudden death?

- Sudden death may be associated with previous symptoms of exertional chest discomfort; dizziness; or prolonged dyspnea with exercise, syncope, and palpitations.
- A family history of premature cardiovascular disease (<50 years), hypertrophic or dilated cardiomyopathy, Marfan syndrome, long QT syndrome, other clinically significant arrhythmias, or sudden death may be elicited.
- Previous recognition of a heart murmur and elevated systemic blood pressure are significant findings.

Mahmood S, Lim L, Akram Y, et al. Screening for sudden cardiac death before participation in high school and collegiate sports. *Am J Prev Med.* 2013;45(1):130–133.

13. What features in the preparticipation sports physical examination identify patients at risk for sudden death?

- **Marfanoid features**: Tall and thin habitus, hyperextensible joints, pectus excavatum, click and murmur suggestive of MVP
- **Pathologic murmurs** (any systolic murmur grade 3/6 or greater, any diastolic murmur)
- **Weak or delayed femoral pulses**
- **Arrhythmia:** Rapid or irregular heartbeat

Ackerman M, Atkins DL, Triedman JK. Sudden cardiac death in the young. *Circulation.* 2016;133(10):1006–1026.

14. Name five disorders in which a screening ECG might identify a subject at risk for sudden death

- **WPW syndrome:** Short PR, delta wave, T-wave abnormalities leading to supraventricular tachycardia (SVT) and ventricular fibrillation
- **Prolonged QT syndrome:** Secondary to congenital channelopathy, electrolyte- or drug-induced abnormality leading to ventricular tachycardia and torsades de pointes
- **Brugada syndrome:** RV conduction delay with profound ST elevation in V_1–V_3 leading to ventricular fibrillation
- **Hypertrophic cardiomyopathy**
- **AV block**

15. What is the likely diagnosis in a 10-year-old Little Leaguer who develops sudden cardiac arrest after being struck in the chest by a batted baseball?

Commotio cordis. This is a life-threatening arrhythmia that occurs as a result of a blunt, nonpenetrating direct blow to the chest. The precordial force is often only low or moderate and typically not associated with structural injury. Ventricular fibrillation is thought to occur when impact is applied during the vulnerable phase of repolarization, 15 to 30 milliseconds before the peak of the T wave. Prompt cardiopulmonary resuscitation (CPR) and defibrillation improve the chance of survival.

Maron BJ, Estes NAM III. Commotio cordis. *N Engl J Med.* 2010;362(10):917–927.

16. In which patients is syncope more likely to be of a cardiac nature?

- Sudden onset without any prodromal period of dizziness or imminent awareness
- Syncope during exercise or exertion
- History of palpitations or abnormal heartbeat before fainting
- Syncope leading to a fall that results in an injury
- Family history of sudden death

17. What arrhythmias may be associated with syncope?

See Table 3.2.

Table 3.2 Syncope

DIAGNOSIS	HISTORY AND PHYSICAL EXAMINATION	ELECTROCARDIOGRAPHIC FINDINGS
WPW	Family history of WPW, known hypertrophic cardiomyopathy, or Ebstein anomaly	Short PR interval, presence of delta waves
Prolonged QT syndrome	Family history of prolonged QT, sudden death, and/or deafness	Borderline QTc = 440–460 msec Prolonged QTc $\geq$460 msec
Atrioventricular block	Myocarditis, Lyme disease, acute rheumatic fever, maternal history of lupus	First-, second-, or third-degree heart block
Arrhythmogenic right ventricular dysplasia	Syncope, palpitations, positive family history	PVCs, ventricular tachycardia, left bundle branch block
Ventricular tachycardia	Most ventricular tachycardia occurs in abnormal hearts; requires extensive evaluation	Ventricular tachycardia

PVCs, Premature ventricular contractions; *QTc,* corrected QT interval; *WPW,* Wolff-Parkinson-White syndrome.
From Feinberg AN, Lane-Davies A. Syncope in the adolescent. *Adolesc Med.* 2002;13:553–567.

KEY POINTS: SYNCOPE MORE LIKELY TO BE OF A CARDIAC NATURE

1. Occurring during exercise
2. Sudden onset without prodromal symptoms or awareness
3. Complete loss of tone or awareness leading to injury
4. Palpitations or abnormal heartbeat noted before event
5. Abnormal heart rate (fast or slow) after event
6. Family history of sudden death

18. What are the most common clinical signs of coarctation of the aorta (Fig. 3.2) in *older* children?

- Differential blood pressure: arms > legs (100%)
- Systolic murmur or bruit in the back (96%)
- Systolic hypertension in the upper extremities (96%)
- Diminished or absent femoral or lower-extremity pulses (92%)

Ing FF, Starc TJ, Griffiths SP, Gersony WM. Early diagnosis of coarctation of the aorta in children: a continuing dilemma. *Pediatrics.* 1996;98(3 Pt 1):378–382.

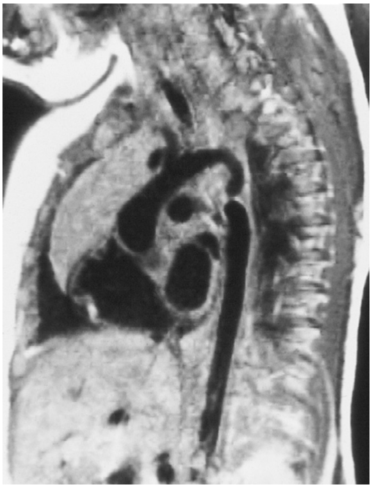

Fig. 3.2 Magnetic resonance imaging of coarctation of the aorta. (From Clark DA. *Atlas of Neonatology.* Philadelphia, PA: W.B. Saunders; 2000:119.)

19. How much does peak exercise affect cardiac output?

Cardiac output is calculated by the formula: *Cardiac output* = *Heart rate* × *Stroke volume* (volume of blood ejected from the left ventricle/beat). Cardiac output at peak exercise will increase up to approximately five times the baseline value. In upright exercise, stroke volume increases early in exercise by 1.5 to 2 times baseline values but then plateaus at that level. Heart rate will also increase early in exercise and will continue to rise up to the maximum predicted value of 200 beats per minute at peak exercise.

20. What cardiac lesions can lead to thrombosis and stroke?

- **Arrhythmias:** Chronic atrial fibrillation, atrial flutter
- **Cardiomyopathies:** Decreased cardiac function is associated with increased risk for thrombus formation; therefore many of these patients are on aspirin or warfarin.
- **Mechanical valves**: These patients require lifelong anticoagulation.
- Patients with **Fontan circulation** are at increased risk for thrombosis.
- Patients with **systemic-to-pulmonary shunts,** such as Blalock-Taussig shunts, are at risk for shunt thrombosis.
- Patients with **Kawasaki disease** with coronary aneurysms are at risk for thrombosis in the coronary arteries.

21. What are two of the more common neuromuscular diseases in which a cardiac consultation is routinely recommended?

- **Duchenne muscular dystrophy** is an X-recessive disease with an abnormality in the dystrophin gene, which leads to muscle necrosis and fibrosis. Although the majority of deaths are due to respiratory insufficiency, death from cardiomyopathy can occur in up to 25% of patients. Symptoms of heart disease are typically hidden by the skeletal myopathy that masks any exercise-induced complaints such as shortness of breath with exertion. Therefore screening echocardiograms and ECGs are recommended for long-term follow-up.
- **Friedrich ataxia** is an autosomal recessive disorder involving a gene encoding frataxin, a mitochondrial protein. Symptoms include ataxia and muscle weakness, typically manifesting by 9 years of age. Cardiac abnormalities include both dilated and concentric cardiomyopathies. Atrial fibrillation and atrial flutter are commonly reported arrhythmias. Because muscle weakness and ataxia will prevent prolonged exertion, periodic echocardiograms and ECGs are recommended.

22. Why are chemotherapeutic agents that use arsenic of cardiac concern?

Arsenic may cause prolonged QT and lead to torsades de pointes (a specific form of ventricular tachycardia in patients with a prolonged QT interval) and ventricular fibrillation. Periodic ECG monitoring is recommended in these patients.

23. What risk is increased for children with Williams syndrome who undergo sedation?

Sudden death. Common cardiovascular abnormalities in Williams syndrome include supravalvular aortic stenosis, peripheral pulmonary branch stenosis, and coarctation of the aorta. Coronary abnormalities include coronary ostial stenosis and diffuse coronary artery stenosis or dilatation. The risk for sudden death is increased in patients with coronary artery abnormalities, including Williams syndrome, as well as those with combined aortic and pulmonary artery stenosis.

24. You see an asymptomatic 5-year-old girl with Turner syndrome, and the parents report that coarctation of the aorta was ruled out when she was 1 month of age. Does she need to return to the cardiologist?

Yes. General categories of cardiac disease in *Turner syndrome* include:

- *Congenital heart disease*: Most commonly coarctation of the aorta, bicuspid aortic valve, aortic stenosis, and hypoplastic left heart syndrome
- *Aortic arch disease*: Coarctation of the aorta, aortic dilatation, and aortic dissection
- *Premature atherosclerosis* associated with the following risk factors: estrogen deficiency, increased incidence of obesity, hypertension, and metabolic syndrome

Guidelines for girls with Turner syndrome recommend cardiac evaluation, including echocardiogram, in all patients at the time of diagnosis. In the absence of a bicuspid aortic valve or significant heart disease, periodic screening for aortic dilatation with echocardiogram and/or cardiac MRI is recommended.

25. Why does an infant suspected of having tuberous sclerosis require a cardiology evaluation?

Tuberous sclerosis affects multiple organs, including the heart. Cardiac problems include rhabdomyomas and an increased frequency of both atrial and ventricular arrhythmias. Rhabdomyomas most commonly occur in the ventricles but may occur in any of the four chambers. They can be detected during fetal scanning and tend to regress spontaneously over the first few years of life. Patients are usually asymptomatic unless the tumors are large or interfere with valve function. Symptomatic patients have been successfully treated with surgery. Effective therapy with sirolimus, an immunosuppressive agent, has been reported in children with large rhabdomyomas.

26. Do cancer survivors who have undergone chemotherapy require long-term cardiac follow-up while they are in remission?

Yes. Long-term cancer survivors have an increased risk for development of a cardiomyopathy. Heart disease is one of the most common causes of noncancerous death in cancer survivors. High-risk groups include females and patients who received higher doses of anthracycline. The Children's Oncology Group recommends ongoing cardiac monitoring while receiving cardiotoxic therapy and every 1 to 5 years after the completion of therapy.

Shah SS, McClellan W, Knowlton JQ, et al. Medium-term assessment of cardiac function in pediatric cancer survivors. Comparison of different echocardiographic methods, cardiac MRI and cardiac biomarker testing in adolescent cancer survivors. *Echocardiography.* 2017;34(2):250–256.

27. What noncardiopulmonary diseases are associated with pulmonary hypertension?

- Chronic thromboembolic disease
- Connective tissue disease
- Human immunodeficiency virus (HIV) infection
- Portal hypertension
- Schistosomiasis
- Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: tumor, fibrosing mediastinitis, chronic renal failure, drug- and toxin-induced

28. What is portopulmonary hypertension?

Approximately 5% of patients with portal hypertension also develop pulmonary hypertension, which is known as *portopulmonary hypertension*. Risk factors for portopulmonary hypertension include female sex, positive serology for autoimmune disease (antinuclear antibodies), autoimmune hepatitis, or chronic hepatitis C infection.

29. Can a patient with heart disease simultaneously be polycythemic and iron deficient?

Yes. Patients with cyanotic heart disease may develop both clinical entities. Initially, as a response to cyanosis, the hematocrit rises. In patients who then develop iron deficiency, the hematocrit may initially remain elevated, but the mean corpuscular volume (MCV) will start to decrease before there is a drop in hematocrit. Detailed studies of iron stores will show low iron and ferritin levels. Children with a history of poor nutrition or blood loss (e.g., previous surgery) are especially at risk for developing iron deficiency.

30. What conditions are associated with an elevated troponin level?

Cardiac troponin is a cardiac-specific protein. Abnormally high serum concentrations can signify damage to the cardiac myocytes. The subtypes cTnI and cTnT are the most commonly measured troponins used by clinical laboratories. cTnI and cTnT are typically elevated in myocardial infarction, ischemia due to hypotension from sepsis, and in up to one-third of children with chronic heart failure. Cardiac troponins can be elevated in both ischemic and nonischemic disease, including acute coronary syndrome, CHF, myocarditis/pericarditis, arrhythmias, heart transplant rejection, myocardial contusion, and after the administration of cardiotoxic drugs.

31. What is the significance of an elevated B-type natriuretic peptide (BNP)?

BNP is a biomarker that is predominantly secreted in the ventricular myocardium in response to increased wall stress. It is secreted as pro-BNP and then cleaved into active and inactive forms. It is useful in determining the role of cardiac involvement in acute cardiopulmonary processes. It can be increased in similar diseases as those listed earlier for troponin (question 30). In addition, BNP can be elevated in patients with diastolic dysfunction and acute respiratory distress syndrome, which do not usually cause increased troponin levels.

Domico M, Allen M. Biomarkers in pediatric cardiac critical care. *Pediatr Crit Care Med.* 2016;17(8 Suppl 1):S215–S221.

CONGENITAL HEART DISEASE

32. How does fetal circulation differ from neonatal circulation?

- Intracardiac and extracardiac shunts are present (i.e., placenta, ductus venosus, foramen ovale, and ductus arteriosus).
- The two ventricles work in parallel rather than in series.
- The right ventricle pumps against a higher resistance than the left ventricle.
- Blood flow to the lung is only a fraction of the RV output.
- The lung extracts oxygen from the blood instead of adding oxygen to the blood.
- The lung continually secretes a fluid into the respiratory passages.
- The liver is the first organ to receive maternal substances (e.g., oxygen, glucose, amino acids).

- The placenta is the major route of gas exchange, excretion, and acquisition of nutritional substances.
- The placenta provides a low-resistance circuit.

Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adams' Heart Disease in Infants, Children, and Adolescents*. 6th ed. Baltimore, MD: Williams & Wilkins; 2001:41–63.

33. What prenatal maternal factors may be associated with cardiac disease in the neonate?

See Table 3.3.

Table 3.3 Prenatal Maternal Factors Associated With Cardiac Disease in Neonates

PRENATAL HISTORICAL FACTOR	ASSOCIATED CARDIAC DEFECT
Diabetes mellitus	Left ventricular outflow obstruction (asymmetric septal hypertrophy, aortic stenosis), D-transposition of great arteries, ventricular septal defect
Lupus erythematosus	Heart block, pericarditis, endomyocardial fibrosis
Rubella	Patent ductus arteriosus, pulmonic stenosis (peripheral)
Alcohol use	Pulmonic stenosis, ventricular septal defect
Aspirin use	Persistent pulmonary hypertension syndrome
Lithium	Ebstein anomaly
Diphenylhydantoin	Aortic stenosis, pulmonary stenosis
Coxsackie B infection	Myocarditis

From Gewitz MH. Cardiac disease in the newborn infant. In Polin RA, Yoder MC, Burg FD, eds. *Workbook in Practical Neonatology.* 3rd ed. Philadelphia, PA: W.B. Saunders; 2001:269.

34. In a cyanotic newborn, what test can help distinguish pulmonary disease from cyanotic CHD?

Hyperoxia test. The infant is placed on 100% oxygen, and an arterial blood gas level is obtained. A PaO_2 of greater than 100 mm Hg is usually achieved in infants with primary lung disease, whereas a PaO_2 of less than 100 mm Hg is characteristic of heart disease. Typically, children with cyanotic heart disease also have a low or normal PCO_2, whereas children with lung disease have an elevated PCO_2. However, the hyperoxia test does not usually distinguish children with cyanotic heart disease from those with persistent pulmonary hypertension.

35. Which congenital heart lesions commonly appear with cyanosis during the newborn period?

Independent pulmonary and systemic circulations (severe cyanosis)

- Transposition of great arteries with an intact ventricular septum

Inadequate pulmonary blood flow (severe cyanosis)

- Tricuspid valve atresia
- Pulmonary valve atresia with intact ventricular septum
- Tetralogy of Fallot
- Severe Ebstein anomaly of the tricuspid valve

Admixture lesions (moderate cyanosis)

- Total anomalous pulmonary venous return
- Hypoplastic left heart syndrome (HLHS)
- Truncus arteriosus

Victoria BE. Cyanotic newborns. In Gessner IH, Victoria BE, eds. *Pediatric Cardiology: A Problem Oriented Approach.* Philadelphia, PA: W.B. Saunders; 1993:101.

KEY POINTS: CARDIAC CAUSES OF CYANOSIS IN THE NEWBORN

1. Transposition of the great arteries
2. Tetralogy of Fallot
3. Truncus arteriosus
4. Pulmonary atresia
5. Total anomalous pulmonary venous return
6. Tricuspid atresia
7. Hypoplastic left heart syndrome

36. How do pulmonary vascular markings on a chest radiograph help in the differential diagnosis of a cyanotic newborn with suspected cardiac disease?

The chest radiograph may help differentiate the types of CHDs. An increase or decrease in pulmonary vascular markings is indicative of the amount of pulmonary blood flow:

Decreased pulmonary markings (diminished pulmonary blood flow)
- Pulmonary atresia or severe stenosis
- Tetralogy of Fallot
- Tricuspid atresia
- Ebstein anomaly

Increased pulmonary markings (increased pulmonary blood flow)
- Transposition of great arteries
- Total anomalous pulmonary venous return
- Truncus arteriosus

37. What ECG findings suggest specific congenital heart conditions?

- **Left axis deviation:** Endocardial cushion defects (both complete AV canal and ostium primum ASDs), tricuspid atresia
- **WPW syndrome (abnormal electrical pathway):** Ebstein anomaly, L-transposition of the great arteries (L-TGA)
- **Complete heart block:** L-TGA, polysplenia syndrome, maternal lupus

38. What chest radiograph findings (Fig. 3.3) are considered characteristic for various CHDs?

- **Boot-shaped heart:** Tetralogy of Fallot
- **Egg-shaped heart:** Transposition of great arteries
- **Snowman silhouette:** Total anomalous pulmonary venous return (supracardiac)

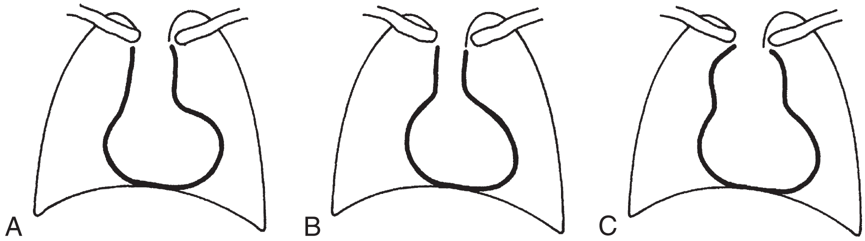

Fig. 3.3 Abnormal cardiac silhouettes. (A) "Boot-shaped" heart seen in cyanotic tetralogy of Fallot or tricuspid atresia. (B) "Egg-shaped" heart seen in transposition of the great arteries. (C) "Snowman" silhouette seen in total anomalous pulmonary artery venous return (supracardiac type). (From Park MK. *Pediatric Cardiology for Practitioners.* 5th ed. Philadelphia, PA: Mosby Elsevier; 2008:68.)

39. What are the common ductal-dependent cardiac lesions?

Ductal-dependent pulmonary blood flow
- Critical pulmonary valve stenosis
- Pulmonary atresia
- Tetralogy of Fallot with severe pulmonary stenosis
- Tricuspid atresia with pulmonary stenosis or pulmonary atresia

Ductal-dependent systemic blood flow
- Coarctation of the aorta
- HLHS
- Interrupted aortic arch

40. What types of CHDs are associated with the right aortic arch?

- Tetralogy of Fallot with pulmonary atresia (50%)
- Truncus arteriosus (35%)
- Classic tetralogy of Fallot (25%)
- Double-outlet right ventricle (25%)
- Single ventricle (12.5%)

Crowley JJ, Oh KS, Newman B, et al. Telltale signs of congenital heart disease. *Radiol Clin North Am.* 1993;31(3):573–582.

41. Which genetic syndromes are most commonly associated with CHD?

See Table 3.4.

Table 3.4 Genetic Syndromes Associated With Congenital Heart Disease

SYNDROME	PERCENTAGE OF PATIENTS WITH CHD	PREDOMINANT HEART DEFECTS
Down	50	ECD, VSD, TOF
Turner	20	COA
Noonan	65	PS, ASD, ASH
Marfan	60	MVP, AoAn, AR
Trisomy 18	90	VSD, PDA
Trisomy 13	80	VSD, PDA
DiGeorge	80	IAA-B, TA
Williams	75	SVAS, peripheral PS

AoAn, Aortic aneurysm; *AR*, aortic regurgitation; *ASD*, atrial sepal defect; *ASH*, asymmetric septal hypertrophy; *CHD*, congenital heart disease; *COA*, coarctation of the aorta; *ECD*, endocardial cushion defect; *IAA-B,* interrupted aortic arch type B; *MVP*, mitral valve prolapse; *PDA*, patent ductus arteriosus; *PS*, pulmonary stenosis; *SVAS*, supravalvular aortic stenosis; *TA*, truncus arteriosus; *TOF*, tetralogy of Fallot; *VSD*, ventricular septal defect.

From Frias JL. Genetic issues of congenital heart defects. In Gessner IH, Victoria BE, eds. *Pediatric Cardiology: A Problem Oriented Approach*. Philadelphia, PA: W.B. Saunders; 1993:238.

42. When does the ductus arteriosus (DA) close in well newborn infants?

The DA begins to constrict shortly after birth. At 24 hours of life, approximately 50% of infants will no longer have detectable flow across the DA by echocardiography. At 72 hours of life, the vast majority of newborn infants no longer have detectable flow across the DA. The DA initially closes functionally, meaning that blood no longer flows across the vessel, but it closes anatomically with fibrosis of the vessel at approximately 2 to 3 weeks of life. Therefore, if the DA closes despite significant CHD, it may be reopened with pharmacologic therapy using prostaglandin E_1 only before full anatomic closure.

43. Describe the clinical manifestations of a large patent ductus arteriosus (PDA)

- Tachypnea and tachycardia
- Abnormal renal function
- Bounding pulses
- Hyperdynamic precordium
- Wide pulse pressure
- Continuous murmur (older child)
- Systolic murmur (premature infant)
- Labile oxygenation (premature infant)
- Apnea (premature infant)

44. How commonly do PDAs occur in premature infants?

They are clinically evident in **40% to 60%** of infants with birth weights of 501 to 1500 g.

45. How can you explain a Pao_2 of more than 400 mm Hg in a blood sample from an umbilical catheter in a newborn with transposition of the great arteries?

A very elevated Pao_2 can be observed if an umbilical vein catheter has passed from the inferior vena cava to the right atrium and into the left atrium. The Po_2 in the left atrium represents the pulmonary venous oxygenation and not the arterial oxygen level. In cyanotic heart disease, the alveolar and pulmonary vein Po_2 values are usually normal. It is the arterial oxygenation concentration that is severely diminished in children with cyanotic heart disease.

46. How do the presenting symptoms of ventricular septal defect (VSD) and ASD differ?

- *VSD*: In an infant with a large VSD, signs of CHF generally appear at 4 to 8 weeks of age, when the pulmonary vascular resistance drops and pulmonary blood flow increases. CHF is due to a large left-to-right shunt and increased pulmonary blood flow and may be associated with failure to thrive or recurrent respiratory infections. The child with a small VSD may have a systolic murmur during the first few weeks of life. These infants do not develop CHF, and spontaneous closure often occurs.

- *ASD:* Most children with an isolated ASD are not clinically diagnosed until they are 3 to 5 years old. Most are asymptomatic at the time of diagnosis. Rarely, infants with an ASD demonstrate signs of CHF during the first year of life.

47. Why is it not always possible to auscultate a murmur in an infant with a VSD on the first day of life?

Murmurs are generated by high-velocity or highly turbulent blood flow. The blood flow across a VSD increases in velocity over the first several days of life as the pulmonary arterial pressure decreases in the transition from fetal to postnatal life. In utero, the pulmonary artery pressure is higher than the systemic arterial pressure and is approximately equal to the systemic pressure shortly after birth. However, the pulmonary artery pressure decreases dramatically over the first several days of life leading to a larger systemic to pulmonary pressure gradient. As the pressure gradient increases, the blood flow across the VSD increases in velocity and the murmur becomes more apparent.

48. What is the primary concern of the pediatric cardiologist if a child with a large VSD is lost to follow-up and comes back after 2 years of age?

Although even a large VSD may close spontaneously in childhood, the child with a large VSD can develop **irreversible pulmonary vascular disease** as a sequela of the long-term increased pulmonary blood flow and **pulmonary hypertension** (Eisenmenger syndrome). This complication is usually preventable if the VSD is closed before 18 to 24 months of age.

49. What are some of the common presenting symptoms in older children with primary pulmonary hypertension?

In the early stages of the disease, children are asymptomatic at rest. Children with primary pulmonary hypertension may present with symptoms such as fatigue, dyspnea, chronic cough, and shortness of breath with exercise. They may also present with chest pain, syncope, and atypical seizures. These symptoms are easily confused with other chronic diseases such as asthma, recurrent pneumonia, or a seizure disorder.

Frank BS, Ivy DD. Diagnosis, evaluation and treatment of pulmonary arterial hypertension in children. *Children (Basel*). 2018;5(4):44–72.

50. What physical examination features are suggestive of pulmonary hypertension?

Physical examination may reveal an RV heave or lift suggestive of RV hypertrophy. The pulmonary component of the second heart sound is usually loud. There may be a 1 to 2/6 diastolic decrescendo murmur of pulmonary insufficiency at the left upper sternal border and a 1 to 2/6 holosystolic murmur of tricuspid insufficiency at the left lower sternal border. Eventually, signs of right heart failure with peripheral edema, neck vein distention, ascites, and hepatomegaly may develop.

51. What are the four structural abnormalities of tetralogy of Fallot?

- Pulmonary stenosis with RV outflow tract obstruction
- VSD
- Aorta overriding the VSD
- RV hypertrophy

52. What occurs during a “Tet spell”?

Tet spells are hypercyanotic episodes that occur in patients with tetralogy of Fallot. The pathophysiology is thought to be related to a change in the balance of systemic-to-pulmonary vascular resistance and/or an increase in RV outflow tract obstruction. Spells may be initiated by events that cause a decrease in systemic vascular resistance (e.g., fever, crying, hypotension) or by events that cause an increase in pulmonary outflow tract obstruction. Both types of events lead to more right-to-left shunting and increased cyanosis. Hypoxia and cyanosis can result in metabolic acidosis and systemic vasodilation, which cause a further increase in cyanosis. Anemia may be a predisposing factor. Although most episodes are self-limited, a prolonged Tet spell can lead to stroke or death; therefore a spell is an indication for surgery.

53. Name two cardiac conditions in which the murmur has disappeared or diminished in intensity and yet the patient is actually worse

- **Tetralogy of Fallot**. The systolic heart murmur represents blood flow across the narrow RV outflow tract. With worsening RV outflow tract obstruction or during a cyanotic spell, less blood crosses the valve, and the heart murmur consequently diminishes and may actually disappear completely.
- **VSD with Eisenmenger syndrome**. The left-to-right shunt across the VSD diminishes because of the increase in pulmonary vascular resistance. The heart murmur lessens and may disappear. A “honeymoon period” with no shunting is then followed by the progression of increased right-to-left shunting and cyanosis. The pulmonary component of the second heart sound begins to increase in intensity, and visible cyanosis and clubbing of the nail beds are often seen.

54. After what age does a presumed peripheral pulmonic branch stenosis murmur deserve more detailed study?

The murmur of peripheral pulmonic branch stenosis—a low-intensity systolic ejection murmur heard frequently in newborns—is the result of the relative hypoplasia of the pulmonary arteries, as well as the acute angle of the branching of pulmonary arteries in the early newborn period. A murmur that persists **beyond 6 months of age** should be investigated.

55. What is the role of pulse oximetry in screening for complex congenital heart disease (CCHD) in asymptomatic infants in the newborn nursery?

Of the approximate 1 in 100 children born with CHD, 25% will have CCHD, defined as a condition that requires surgical or catheter intervention in the first year of life. When the diagnosis is delayed, there can be a significant impact on morbidity and mortality. These delays can occur because of limitations of the physical examination (particularly in those lesions without distinct murmurs), difficulty in identifying cyanosis in anemic or dark-pigmented neonates, and early hospital discharge for ductal-dependent lesions when the DA has not yet closed. Discharged infants may later present *in extremis* with sudden and profound clinical worsening, including shock, due to changes in pulmonary vascular resistance and ductal closure.

Universal pulse oximetry screening of newborns, ideally done after 24 hours, is now recommended by the American Academy of Pediatrics (AAP) as a means of identifying infants with CCHD before leaving the nursery. The rationale is based on the fact that hypoxemia is present to some degree in the majority of cases of CCHD. The screen is felt to have a sensitivity of 60% to 70% for CCHD, so a normal screen does not rule out heart disease.

56. What is the AAP screening protocol for CCHD using pulse oximetry?

Oxygen saturation is measured in the right hand and either foot. The screen is failed if oxygen level is $<90\%$ in either limb. If oxygen saturation is $\geq 90\%$ and $<95\%$ in both limbs or there is $>3\%$ difference between the hand and foot, repeat testing should be done in 1 hour. If persistent, the screen is failed. For a failed screen, cardiology consultation is recommended, and an echocardiography is generally indicated. Screening should be completed no earlier than 24 hours after birth to lessen false-positive results.

Plana MN, Zamora J, Suresh G, et al. Pulse oximetry screening for critical congenital heart defects. *Cochrane Database Syst Rev.* 2018;3:CD011912.

Mahle WT, Martin GR, Beekman RH III, et al. Endorsement of Health and Human Services recommendation for pulse oximetry screening for critical congenital heart disease. *Pediatrics.* 2012;129(1):190–192.

57. Which ductal-dependent lesions are the AAP's primary targets for screening with the use of pulse oximetry?

- HLHS
- Pulmonary atresia
- Tetralogy of Fallot
- Total anomalous pulmonary venous return
- Transposition of the great arteries
- Truncus arteriosus

58. What CHDs may remain unsuspected even after normal newborn oximetry screening?

The presence of a normal physical examination and normal oximetry screening test will identify up to 75% of infants with critical CHD. The most frequently missed lesions in several studies were those due to obstruction of the aorta, such as coarctation of the aorta or an interruption of the aortic arch. Significant, but not immediately life-threating, lesions that are not ductal dependent are missed more often: for example, VSD, ASD, and PDA.

59. What are the risks for recurrence of common heart defects in a second child?

The risk for CHD in pregnancies after the birth of one affected child is about 1% to 4%. With two affected first-degree relatives, the risk is about 10%. With three affected children, the family may be considered at even higher risk.

60. Can you think of a "handy" way to remember the congenital cyanotic heart diseases?

See Fig. 3.4.

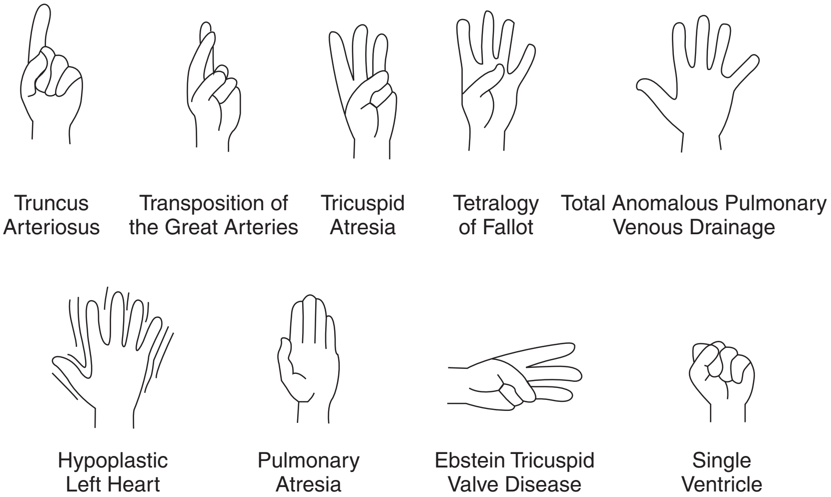

Fig. 3.4 Congenital cyanotic heart disease hand signatures.

61. What types of congenital heart lesions are associated with congenital diaphragmatic hernia?

Approximately 10% to 15% of infants with congenital diaphragmatic hernia also have structural hemodynamically significant heart disease. In one review of 2636 infants with congenital diaphragmatic hernia, approximately 10% of infants had significant heart disease, which excluded PDA, patent foramen ovale, and ASDs.

Significant lesions included:

- VSD: 42%
- Aortic arch obstruction: 15%
- Univentricular anatomy: 14%
- Tetralogy of Fallot variants: 11%
- Double outlet right ventricle: 3%
- Pulmonary stenosis: 3%
- Transposition of the great arteries: 2.5%
- Others: 6%

Graziano JN. Cardiac anomalies in patients with congenital diaphragmatic hernia and their prognosis: a report from the Congenital Diaphragmatic Hernia Study Group. *J Pediatr Surg.* 2005;40(6):1045–1049.

62. What are four genetic syndromes associated with café au lait spots and heart disease?

Café au lait spots are typically light-brown, flat birthmarks, which can increase in size and number over time. Four syndromes in which café au lait spots are characteristic findings and their associated cardiac lesions are as follows:

- **Neurofibromatosis type 1**
  - Coarctation of the aorta
- **LEOPARD syndrome** (multiple lentigines syndrome)
  - Heart block, pulmonary stenosis, aortic stenosis, cardiomyopathy
- **Noonan syndrome**
  - Pulmonary stenosis, cardiomyopathy, coronary artery dilatation
- **Tuberous sclerosis**
  - Rhabdomyomas, arrhythmias

63. Why should children with CCHD undergo routine screening for developmental disorders?

Children with CCHD have an *increased risk* for developmental disorders in multiple domains, including intelligence, academic achievement, language skills, visual perception, attention, executive functioning, and fine and gross motor skills in addition to various types of psychosocial difficulties. All children should be screened for developmental disabilities in an ongoing manner by the primary pediatric provider. Early referral for formal testing and intervention services should be done to optimize socialization and learning skills.

64. Which risk factors increase the likelihood of neurodevelopmental disorders in children with CHD?

The incidence of developmental disorders is higher in children with more complex CHD, such as HLHS, tetralogy of Fallot, and transposition of the great arteries, comp[illegible]d with less complex conditions, such ASDs or uncomplicated VSDs.

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For personal use only. No other uses w[illegible]020. Elsevier Inc. All rights reserved.

Developmental problems are also more common in children who undergo open heart surgery in the neonatal period compared with later in life. Comorbidities that increase the risk for developmental disorders include prematurity, antenatal growth restriction, recognition of developmental problems early in infancy, history of mechanical support (extracorporeal membrane oxygenation [ECMO] or ventricular assist device), heart transplantation, CPR, prolonged hospitalization (>2 weeks), and/or perioperative seizures.

Marino BS, Lipkin PH, Newburger JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation.* 2012;126(9):1143–1172.

CONGESTIVE HEART FAILURE

65. What clinical signs and symptoms are associated with CHF in children?

These may be grouped into three categories:

- **Signs or symptoms of impaired myocardial performance:** cardiomegaly, tachycardia, gallop rhythm, cold extremities or mottling, growth failure, sweating with feeding, pallor
- **Signs or symptoms of pulmonary congestion:** tachypnea, wheezing, rales, cyanosis, dyspnea, cough
- **Signs or symptoms of systemic venous congestion:** hepatomegaly, neck vein distention, peripheral edema (seen in the older patient)

66. How is heart size assessed in older children?

Cardiothoracic (CT) ratio: This is derived by comparing the largest transverse diameter of the heart with the widest internal diameter of the chest: CT ratio = (A + B) / C, as shown in Fig. 3.5. A CT ratio of >0.5 indicates cardiomegaly.

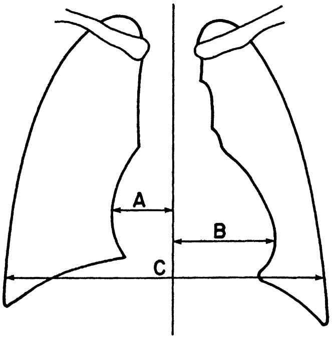


Fig. 3.5 The cardiothoracic ratio is obtained by dividing the largest horizontal diameter of the heart *(A + B)* by the longest internal diameter of the chest *(C).* (From Park MK. *Pediatric Cardiology for Practitioners.* 5th ed. Philadelphia, PA: Mosby Elsevier; 2008:66.)

67. In infancy, how does the likely cause of CHF vary by age?

See Table 3.5.

Table 3.5 Causes of Congestive Heart Failure

AGE OF ONSET	CAUSE
At birth	HLHS with restrictive foramen ovale
	Volume overload lesions
	Severe tricuspid or pulmonary insufficiency (i.e., severe Ebstein, tetralogy of Fallot with absent pulmonary valve)
	Large systemic arteriovenous fistula
	Arrhythmia
0-7 days	TGA and VSD
	PDA in small premature infants
	HLHS
	TAPVR, particularly those with pulmonary venous obstruction
	Systemic arteriovenous fistula
	Critical AS or PS

Continued on following page

Table 3.5 Causes of Congestive Heart Failure (*Continued*)

AGE OF ONSET	CAUSE
1-6 wk	COA isolated or with associated anomalies
	Critical AS
	Large left-to-right shunt lesions (VSD, PDA, AVC)
	All other lesions previously listed
6 wk–4 mo	Large VSD
	Large PDA
	Others such as anomalous left coronary artery from the PA

AS, aortic stenosis; *AVC*, atrioventricular canal; *COA*, coarctation of the aorta; *HLHS*, hypoplastic left heart syndrome; *PA*, pulmonary artery; *PDA*, patent ductus arteriosus; *PS*, pulmonary stenosis; *TAPVR*, total anomalous pulmonary venous return; *TGA*, transposition of the great arteries; *VSD*, ventricular septal defect.

Adapted from Park, MK. *Pediatric Cardiology for Practitioners.* 5th ed. St. Louis, MO: Mosby; 2008:462.

KEY POINTS: COMMON CARDIAC CAUSES OF CONGESTIVE HEART FAILURE IN A 6-WEEK-OLD INFANT

1. Ventricular septal defect
2. Atrioventricular canal
3. Patent ductus arteriosus
4. Coarctation of the aorta

68. What are the typical ages for the presentation of CHF with CHD?

As a general rule, large-volume overload lesions (e.g., Ebstein anomaly or AV malformations) present soon after birth, ductal-dependent lesions present during the few days of life when the ductus closes, and lesions with significant left-to-right shunting present over the first 1 to 2 months as the pulmonary vascular resistance falls and leads to increased systemic-to-pulmonary shunting.

69. If a newborn infant develops CHF and cardiomegaly but no heart murmur is heard, what is the differential diagnosis?

- Myocarditis
- Cardiomyopathy as a result of asphyxia or sepsis
- Glycogen storage disease (Pompe disease)
- Cardiac arrhythmia: SVT, congenital heart block, atrial flutter
- AV malformations (e.g., liver, vein of Galen)

70. If a child develops CHF and cardiomegaly after the newborn period but no murmur is heard, what is the differential diagnosis?

Myocardial diseases

- Myocarditis (viral or idiopathic)
- Glycogen storage disease (Pompe disease)
- Endocardial fibroelastosis

Coronary artery diseases resulting in myocardial insufficiency

- Anomalous origin of left coronary artery from pulmonary artery
- Kawasaki syndrome (acute vasculitis of infancy and early childhood)
- Calcification of the coronary arteries

CHD with severe heart failure

- Coarctation of the aorta in infants
- Ebstein anomaly (may have gallop rhythm)

ELECTROCARDIOGRAMS AND ARRHYTHMIAS

71. How does the ECG of a term infant differ from that of the older child?

- *Birth:* At birth, the ECG reflects RV dominance. The QRS complex consists of a tall R wave in the right precordial leads (V_1 and V_2) and a large S wave in the left precordial leads (V_5 and V_6). The QRS axis is also rightward (90 to 180 degrees). T waves are initially variable with relatively low voltage. They are upright in anterior precordial leads (V_1 to $V_{3\text{-}4}$), invert by 7 days of age, and can remain inverted until about 12 to 13 years.

- *Toddler age (2 to 4 years):* There is an axis shift from the right to the normal quadrant, and the R wave diminishes over the right precordial leads. The S wave disappears from the left precordium.
- *School age:* At this age, the ECG has a nearly adult pattern, with a small R and a dominant S in the right precordial leads and an axis in the normal quadrant.

Price A, Kaski J. How to use the paediatric ECG. *Arch Dis Child Educ Pract Ed.* 2014;99(2):53–60.

72. What are the characteristic features of the ECG of a premature infant?

In the premature infant, there is less RV dominance. The R wave may be small in the right precordial leads, and there may be no significant S wave over the left precordium. The electrical axis is often in the normal quadrant (0 to 90 degrees).

73. What ECG abnormalities are associated with potassium and calcium imbalances?

See Fig. 3.6.

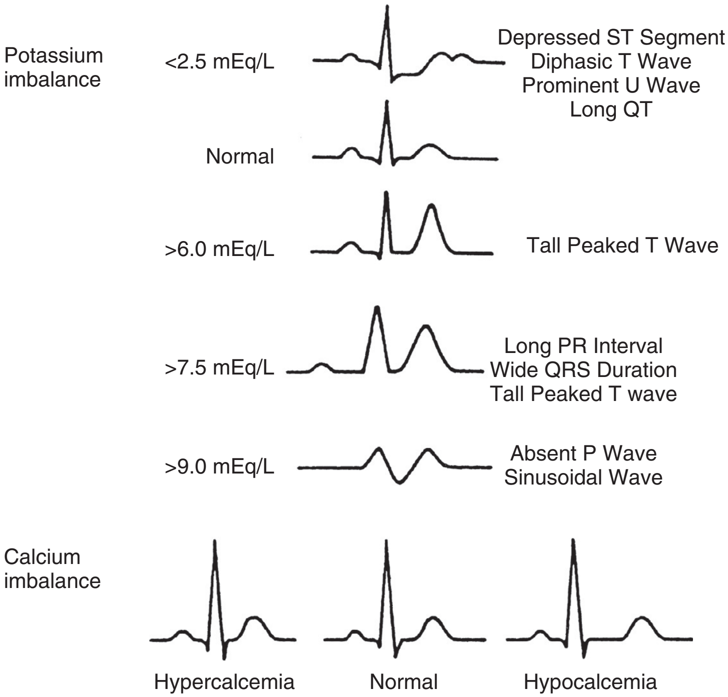

Potassium imbalance
<2.5 mEq/L
Depressed ST Segment
Diphasic T Wave
Prominent U Wave
Long QT
Normal
>6.0 mEq/L
Tall Peaked T Wave
>7.5 mEq/L
Long PR Interval
Wide QRS Duration
Tall Peaked T wave
>9.0 mEq/L
Absent P Wave
Sinusoidal Wave
Calcium imbalance
Hypercalcemia
Normal
Hypocalcemia

Fig. 3.6 Electrocardiogram abnormalities associated with potassium and calcium imbalances. (From Park MK, Guntheroth WG. *How to Read Pediatric ECGs.* 3rd ed. St. Louis, MO: Mosby; 1992:106-107.)

74. What is the difference between a QT interval and a corrected QT interval (QTc)?

The QT interval represents the time required for ventricular depolarization and repolarization. It begins at the onset of the QRS complex and continues through the end of the T wave. This interval varies with the heart rate. The QTc adjusts for heart rate differences. As a rule, a prolonged QTc interval is diagnosed when the QTc exceeds 0.44 second using the following formula, known as the *Bazett formula,* with RR representing the interval from the onset of the preceding QRS complex to the onset of the next QRS complex:

$$QT_c = QT\ (\text{in seconds}) / \sqrt{RR}\ \text{interval}\ (\text{in seconds})$$

75. What causes a prolonged QT interval?

Congenital long QT syndrome

- Hereditary form: ion channelopathies (genetic defects in specific potassium and sodium channel genes), Jervell and Lange-Nielsen syndrome (associated with deafness), Romano-Ward syndrome
- Sporadic type

Acquired long QT syndrome
- Drug induced (especially some antiarrhythmic agents, tricyclic antidepressants, phenothiazines)
- Metabolic and electrolyte abnormalities (hypocalcemia, hypokalemia, very-low-energy diets)
- Central nervous system and autonomic nervous system disorders (especially after head trauma or stroke)
- Cardiac disease (myocarditis, coronary artery disease)

Behere SP, Shubkin CD, Weindling SN. Recent advances in the understanding and management of long QT syndrome. *Curr Opin Pediatr.* 2014;26(6):727–733.

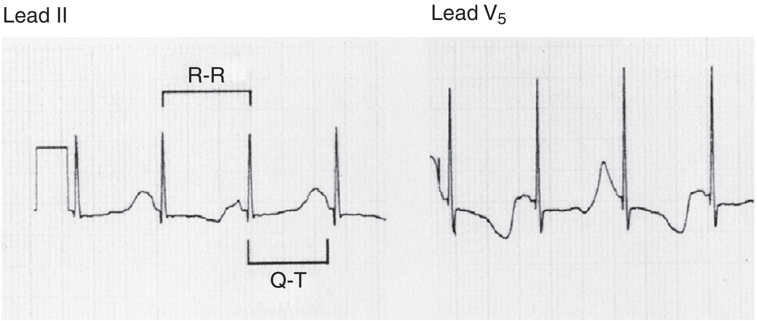
SADS (Sudden Arrhythmia Death Syndromes) Foundation. www.sads.org. (Available is a list of drugs that should be avoided in patients with long QT syndrome.) Accessed June 5, 2019.

KEY POINTS: ELECTROCARDIOGRAMS

1. Compared with adults, newborns and infants normally have right ventricular dominance.
2. When a child reaches school age, the ECG achieves a nearly adult pattern with a small R and a dominant S in the right precordial leads and an axis in the normal quadrant.
3. Electrolyte abnormalities (hypocalcemia and hypokalemia) can prolong the QT interval.
4. QT intervals must be corrected for heart rates.

76. What ECG features are found in the long QT syndromes?

These are disorders of repolarization with prolongation of the QT interval, corrected for heart rate (QTc). Other ECG findings are relative bradycardia, T-wave abnormalities, and episodic ventricular tachyarrhythmias, particularly torsades de pointes (Fig. 3.7).



$$\text{Bazett formula: QTc} = \frac{\text{QT}}{\sqrt{\text{R-R}}}$$

Fig. 3.7 Long QT syndrome, leads II and V5. Note the long QT interval and T-wave alternans (alternating upright and downgoing T waves). (From Towbin JA. Molecular genetic basis of sudden cardiac death. *Pediatr Clin North Am.* 2004;51:1230, Fig. 1.)

77. What characterizes torsades de pointes?

From the French for "to turn on a point," this is a ventricular tachycardia of varying forms characterized by abrupt changes in amplitude and polarity (Fig. 3.8). It is a pathologic tachyarrhythmia seen in patients with prolonged QT syndromes and the use of certain drugs (e.g., cisapride, thioridazine).

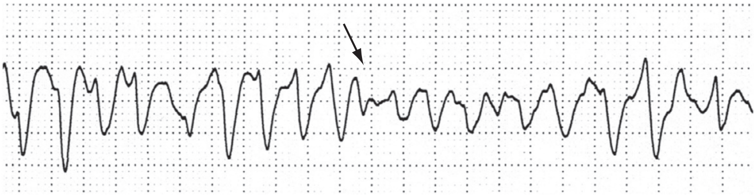


Fig. 3.8 Torsades de pointes polymorphic ventricular tachycardia. Note the phase change *(arrow)* with change in QRS polarity. (From Samson RA, Atkins RA. Tachyarrhythmias and defibrillation. *Pediatr Clin North Am.* 2008;55:891.)

78. What are the ECG findings in patients with complete heart block?

The atrial and ventricular activities are entirely independent. P waves are regular, and QRS complexes are also regular, with a rate slower than the P rate (Fig. 3.9).

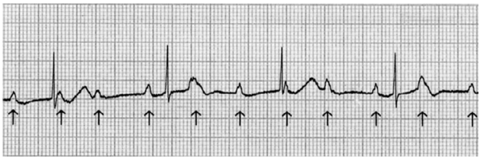


Fig. 3.9 Complete heart block. Tracing demonstrates atrial activity *(arrows)* independent of slower ventricular rhythm. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis.* 4th ed. St. Louis, MO: Mosby; 2002:144.)

79. How abnormal are premature atrial contractions?

Premature atrial beats are usually benign, with the exception of patients with an electrical or anatomic substrate for SVT or atrial flutter.

80. How does SVT in children differ from physiologic sinus tachycardia?

SVT typically has the following features:

- Sudden onset and termination rather than a gradual change in rate
- Persistent ventricular rate of >180 beats/minute
- Fixed or almost-fixed RR interval on ECG
- Abnormal P-wave shape or axis or absent P waves
- Little change in heart rate with activity, crying, or breath holding

81. Name the two most common mechanisms of SVT

- **WPW syndrome** (due to an accessory bypass tract)
- **AV nodal reentry**

82. What are some of the causes of a wide QRS complex?

- Premature ventricular contraction
- Ventricular tachycardia
- Premature atrial contraction with aberrant conduction
- SVT with aberrant conduction
- Bundle branch blocks
- Preexcitation syndromes (WPW syndrome)
- Electrolyte abnormalities
- Myocarditis
- Cardiomyopathy
- Electronic ventricular pacemaker

83. What vagal maneuvers are used to treat paroxysmal SVT in children?

Infants

- Place plastic bag filled with crushed ice over forehead and nose
- Induce gag with tongue blade

Older children and adolescents

- Previous methods
- Unilateral carotid massage
- Valsalva maneuver (abdominal straining while holding breath)

In general, the Valsalva maneuver and carotid massage are not as effective for children <4 years. Ocular pressure is not recommended because it has been associated with retinal injury. Vagal stimulation slows conduction and prolongs refractoriness of the AV node, thereby interrupting the reentrant circuit.

84. In addition to vagal maneuvers, what treatments are used acutely for managing SVT?

If a patient's clinical condition has deteriorated, synchronized direct-current **cardioversion** is indicated. In patients who are stable and for whom vagal maneuvers have failed, **adenosine** has replaced digoxin and verapamil as the first drug of choice. An initial bolus of 0.05 to 0.1 mg/kg (maximum 6 mg/dose) followed by a normal saline bolus will exert an effect in 10 to 20 seconds by slowing conduction through the AV node. If this is ineffective, the dose can be increased in increments of 0.1 mg/kg every 1 to 2 minutes to a maximum of 0.3 mg/kg (maximum 12 mg/dose). The usual starting dose in adults is 6 mg and then 12 mg if the tachycardia persists.

85. Why should an electrographic tracing (preferably with multiple leads) be carried out while administering intravenous adenosine?

Adenosine is used to convert reentrant SVT to sinus rhythm. During the conversion, observation of the termination of the arrhythmia on ECG can often reveal the mechanism of the tachycardia. If the tachycardia does not terminate, other information can be obtained from the ECG, including:

- The tachycardia is atrial in origin; one can observe varying degrees of AV block with the atrial tachycardia persisting (e.g., atrial flutter).
- The tachycardia is junctional or ventricular with 1:1 ventriculoatrial (VA) conduction; adenosine may induce VA block with VA dissociation.
- The tachycardia terminated and was immediately restarted by a premature atrial beat.

86. Which children are candidates for transcatheter ablation techniques for SVT?

Ablation therapy is used most commonly in children with arrhythmias that are refractory to medical management and in those with life-threatening symptoms or possible lifelong medication requirements. Ablation is now commonly performed in children who are symptomatic from WPW or AV nodal reentrant tachycardia. Recommendations vary with the age of the patient, the severity of the arrhythmia, the type of lesion, the difficulty with medical control of the rhythm disorder, and the skill of the operator.

87. What is the lethal arrhythmia of WPW syndrome?

The lethal arrhythmia in patients with WPW is **atrial fibrillation with a rapid ventricular response that degenerates into ventricular fibrillation**. The rate of the ventricular response in these patients is dependent on the effective refractory period of the accessory pathway and not the AV node. This can result in ventricular rates of 250 to 300 beats per minute. After ablation of the accessory pathway, these patients are no longer at risk for atrial fibrillation.

88. How is WPW syndrome diagnosed on the baseline ECG?

An accessory pathway bypasses the AV node, thereby resulting in early ventricular depolarization (preexcitation). It is the most common cause of SVT in children. In infants and younger children with rapid heart rates, the delta wave may not be as evident. Classic findings (Fig. 3.10) include:

- Slurring of the initial portion of the QRS (delta wave)
- PR interval of <100 msec
- QRS duration of >80 msec
- Nonspecific ST and T wave changes
- Additional clues that may be suggestive of WPW include the following:
  - No Q wave in left chest leads
  - Left axis deviation

Perry JC, Giuffre RM, Garson A Jr. Clues to the electrocardiographic diagnosis of subtle Wolff-Parkinson-White syndrome in children. *J Pediatr.* 1990;117(6):871–875.

Wolff-Parkinson-White Preexcitation

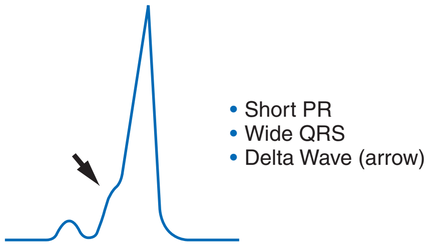


Fig. 3.10 Wolf-Parkinson-White preexcitation. (From Goldberger AL, Goldberger AD, Shvikin A. *Clinical Electrocardiography: A Simplified Approach.* 8th ed. Philadelphia, PA: Elsevier Saunders; 2013:208.)

INFECTIOUS AND INFLAMMATORY DISORDERS

89. How many blood cultures should be obtained in patients suspected of bacterial endocarditis?

At least **three** separate blood cultures should be obtained. The use of multiple sites may decrease the likelihood of mistaking a contaminant for the true etiologic agent.

90. Why might properly collected blood cultures be negative in the setting of clinically suspected bacterial endocarditis?

- Prior antibiotic use
- Endocarditis may be right-sided
- Nonbacterial infection: fungal (e.g., *Aspergillus, Candida*) or unusual organisms (e.g., *Bartonella, Rickettsia*, *Chlamydia*)
- Unusual bacterial infection: slow-growing organisms (e.g., *Brucella, Haemophilus*) or anaerobes
- Lesions may be mural or nonvalvular (i.e., less likely to be hematogenously seeded)
- Nonbacterial thrombotic endocarditis (sterile platelet–fibrin thrombus formations after endocardial injury)
- Incorrect diagnosis

Starke JR. Infective endocarditis. In Cherry JD, Harrison GJ, Kaplan SL, et al., eds. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia, PA: Saunders Elsevier; 2014:358.

91. When is antibiotic prophylaxis for a dental procedure recommended?

In an updated statement in 2017, the American Heart Association and the American College of Cardiology advised dental antibiotic prophylaxis for patients with the following high risk conditions:

- Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts
- Prosthetic materials used for cardiac valve repair, such as annuloplasty rings and chords
- Previous infective endocarditis.
- Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device
- Cardiac transplant with valve regurgitation due to a structurally abnormal valve

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Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. *Circulation*. 2017;135(25):e1159–e1195.

92. How reliable is the echocardiogram for diagnosing bacterial endocarditis (BE)?

Echocardiography can sometimes identify an intracardiac mass that is attached either to the wall of the myocardium or to part of the valve. Although the yield of echocardiography for diagnosing BE is low, the likelihood of a positive finding is increased under certain conditions (e.g., indwelling catheters, prematurity, immunosuppression, evidence of peripheral embolization). BE is a clinical and laboratory diagnosis (physical examination and blood cultures, respectively) and not solely an "echocardiographic" diagnosis. A negative study does not rule out BE.

93. What complications are associated with infective carditis?

Complications of infective endocarditis can be classified as cardiac and noncardiac. *Cardiac complications* include CHF, new or progressive valve dysfunction, increased valve regurgitation, periannular extension of the infection, rupture of the sinus of Valsalva, myocardial dysfunction, obstruction of a conduit, and, rarely, septic emboli to the coronary artery. *Noncardiac complications* include emboli to cerebral, renal, or any arterial bed. Stroke, pulmonary emboli, meningitis, seizures, and immune complex vasculitis may also occur.

94. What increases the risk for complications in patients with infective endocarditis?

Complications are increased in children with left-sided endocarditis (e.g., mitral or aortic valve endocarditis), prosthetic cardiac valves, previous endocarditis, prolonged clinical symptoms (>3 months), cyanotic CHD, systemic-to-pulmonary artery shunts, and poor clinical response to antimicrobial therapy. Other considerations include the size and location of the vegetation, acute onset of AV block, type of organism, fungal infections, and infective endocarditis in children <2 years of age.

95. When should myocarditis be suspected?

The presenting symptoms of myocarditis can be variable, ranging from subclinical to rapidly progressive CHF. It should be considered in any patient who experiences unexplained heart failure. Clinical signs include **tachycardia out of proportion to fever, tachypnea, a quiet precordium, muffled heart tones**, **gallop rhythm without murmur**, and **hepatomegaly**.

Pettit MA, Koyfman A, Foran M. Myocarditis. *Pediatr Emerg Care.* 2014;30(11):832–835.

96. What conditions are associated with the development of myocarditis?

Infections

- *Bacterial*: Diphtheria
- *Viral*: Coxsackie B (most common), coxsackie A, HIV, echoviruses, rubella
- *Mycoplasmal*
- *Rickettsial*: Typhus

- *Fungal*: Actinomycosis, coccidioidomycosis, histoplasmosis
- *Protozoal*: Trypanosomiasis (Chagas disease), toxoplasmosis

Inflammatory

- Kawasaki disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Eosinophilic myocarditis

Chemical and physical agents

- Radiation injury
- Drugs: Doxorubicin
- Toxins: Lead
- Animal bites: Scorpion, snake

97. A child visiting from South America presents with symptoms including unilateral eye swelling and new-onset acute CHF. What is a likely diagnosis?

Acute myocarditis as a result of **Chagas disease** (American trypanosomiasis) is likely. *Romaña sign* is unilateral, painless, violaceous, palpebral edema often accompanied by conjunctivitis. It is seen in 25% to 50% of patients with early Chagas disease in endemic areas. The swelling occurs near the bite site of the parasitic vector, the reduviid bug. Chagas disease, a protozoan infection due to *Trypanosoma cruzi*, is a common cause of acute and chronic myocarditis in Central and South America.

98. What are the common clinical symptoms and signs of pericarditis?

- *Symptoms:* Chest pain, fever, cough, palpitations, irritability, abdominal pain
- *Signs:* Friction rub, pallor, pulsus paradoxus, muffled heart sounds, neck vein distention, hepatomegaly

99. What is the position of comfort in the patient with pericarditis?

The typical patient with pericarditis prefers **to sit up and lean forward.**

100. What is the leading cause of identifiable acquired heart disease in the developed world?

Kawasaki disease, also called *mucocutaneous lymph node syndrome.* Kawasaki disease is a multisystem disease characterized by vasculitis of small and medium-sized blood vessels. If untreated, the condition can lead to coronary artery aneurysms and myocardial infarction. A high index of suspicion is important, because Kawasaki disease has replaced acute rheumatic fever as the leading cause of identifiable acquired heart disease in the developed world.

McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease. *Circulation.* 2017;135(17):e927–e999.

Kawasaki Disease Foundation. www.kdfoundation.org. Accessed January 10, 2020.

101. What are the principal diagnostic criteria for Kawasaki disease?

The presence of fever and at least four of five other features are needed for the classic diagnosis. The mnemonic **My HEART** may be helpful:

- **M**ucosal changes, especially oral and upper respiratory; dry and chapped lips; “strawberry tongue”
- **H**and and extremity changes, including reddened palms and soles and edema; desquamation from fingertips and toes is a later finding (second week of illness)
- **E**ye changes, primarily a bilateral conjunctival infection without discharge
- **A**denopathy that is usually cervical, often unilateral, and $\geq$1.5 cm in diameter
- **R**ash that is usually a truncal exanthem without vesicles, bullae, or petechiae
- **T**emperature elevation, often to 40°C (104°F) or above, lasting for $>$5 days

102. What makes incomplete (or atypical) Kawasaki disease incomplete (or atypical)?

Incomplete (or atypical) Kawasaki disease does not fulfill sufficient diagnostic criteria for classic Kawasaki disease. The clinical features are similar but differ in number. In incomplete disease, children have fever but fewer than four signs of mucocutaneous inflammation. About 15% to 20% of reported Kawasaki cases are of the incomplete variety, particularly in children $<$1 year. Despite not meeting the classic criteria, children with incomplete Kawasaki disease remain at risk for the same coronary artery changes.

Manlhiot C, Christie E, McCrindle BW, et al. Complete and incomplete Kawasaki disease: two sides of the same coin. *Eur J Pediatr.* 2012;171(4):609–611.

103. Which diagnostic manifestation of Kawasaki disease is most commonly absent?

Cervical lymphadenopathy, in both complete and incomplete Kawasaki disease, is most commonly absent. Up to 90% of patients with incomplete disease and 40% to 50% of those who meet classic criteria for Kawasaki disease do not have adenopathy.

Fukushige J, Takahashi N, Ueda Y, et al. Incidence and c[illegible]l features of incomplete Kawasaki disease. *Acta Paediatr.* 1994;83(10):1057–1060.

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104. What laboratory tests are often abnormal in the first 7 to 10 days of Kawasaki disease?

- **Complete blood count:** Fifty percent of patients have an elevated white blood cell count ($>$15,000) with neutrophilia and a progressive normochromic, normocytic anemia. Platelet count increases and peaks in the second to third week of illness.
- **Urinalysis:** Pyuria without bacteriuria (culture usually negative)
- **Acute phase reactants:** C-reactive protein and erythrocyte sedimentation rate are significantly elevated in 80%.
- **Blood chemistry:** Mild increase in hepatic transaminases, low serum sodium, protein, and/or albumin
- **Cerebrospinal fluid:** Pleocytosis (usually lymphocytic) with normal protein and glucose

105. What is the typical age of children with Kawasaki disease?

Eighty percent of cases occur between the ages of 6 months and 5 years. However, cases can occur in infants and teenagers. Both of these groups appear to be at increased risk for developing coronary artery sequelae. The diagnosis is often delayed, particularly in infants, because signs and symptoms of the illness may be incomplete or subtle. Of note, the condition is exceedingly rare in adults.

KEY POINTS: DIAGNOSTIC FEATURES OF KAWASAKI DISEASE

1. Erythema of oral cavity and dry, chapped lips
2. Conjunctivitis: Bilateral and without discharge
3. Edema and erythema and/or desquamation of hands and feet
4. Cervical lymphadenopathy
5. Polymorphous exanthem on trunk, flexor regions, and perineum
6. Fever, often up to 40°C (104°F), lasting $\geq$5 days
7. No other identifiable diagnostic entity to explain signs and symptoms
8. Incomplete Kawasaki disease (fever but fewer than four of the other criteria) is common in children $<$1 year of age.

106. Why should all children with Kawasaki disease receive intravenous immunoglobulin (IVIG) therapy?

IVIG has been demonstrated to decrease the incidence of coronary artery abnormalities in children with Kawasaki disease. Additionally, fever and laboratory indices of inflammation resolve more quickly after treatment. The most common dosing is a single infusion over 8 to 12 hours of 2 g/kg. In children who remain febrile 36 hours after the first infusion, a second dose of 2 g/kg is recommended. When administered 5 to 10 days after the start of fever, IVIG improves outcome, with coronary artery dilation developing in less than 5% of patients and giant coronary aneurysms developing in less than 1% of patients. At present, there are no reliable means of predicting which children with Kawasaki disease will develop coronary artery abnormalities. Therefore all children with Kawasaki disease should receive parental immunoglobulin.

Lo MS, Newburger JW. Role of intravenous immunoglobulin in the treatment of Kawasaki disease. *Int J Rheum Dis.* 2018;21(1):64–69.

107. Is aspirin therapy of benefit for children with Kawasaki disease?

Moderate-dose (30 to 50 mg/kg/day) or high-dose aspirin (80 to 100 mg/kg/day), divided into doses taken every 6 hours, is effective for decreasing the degree of fever and discomfort in patients during the acute stages of illness. It is unclear whether high-dose aspirin has an additive effect for decreasing the incidence of coronary artery abnormalities when used in conjunction with IVIG. Aspirin may be beneficial when administered in low doses after the resolution of fever because of its effects on platelet aggregation and prevention of the thrombotic complications seen in children with Kawasaki disease. Therefore, when fever has been absent for 48 hours, the patient is switched to aspirin in low doses (3 to 5 mg/kg/day), which is continued for about 6 to 8 weeks. If a follow-up echocardiogram at that time reveals no coronary abnormalities, therapy is usually discontinued. If abnormalities are present, therapy is continued indefinitely.

108. What is the likelihood of a patient developing coronary artery pathology *with* and *without* treatment for Kawasaki disease?

In 30% to 50% of patients, a mild diffuse dilation of coronary arteries begins 10 days after the start of fever. If untreated, 20% to 25% of these will progress to true aneurysms (Fig. 3.11). In about 1% of cases, giant aneurysms ($>$8 mm diameter) develop, which may heal with stenosis and lead to myocardial ischemia. With IVIG therapy, the incidence of aneurysms is reduced to less than 5%.

Harnden A, Tulloh R, Burgner D. Kawasaki disease. *BMJ.* 2014;349:g5336.

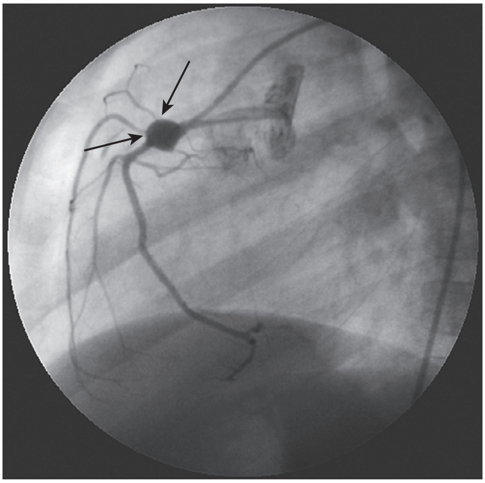

Fig. 3.11 Lateral view of coronary angiogram showing right coronary artery with saccular aneurysm (arrows). (From Vetter VL, ed. *Pediatric Cardiology: The Requisites in Pediatrics.* Philadelphia, PA: Mosby; 2006:135.)

109. Does a normal echocardiogram in a child with an unexplained fever rule out Kawasaki disease?

No. A normal echocardiogram during the initial stages of Kawasaki disease does not effectively rule out the disease. Aneurysms of the coronary artery are not typically present in the early stages of the disease. An initial echocardiogram will establish a baseline for subsequent evaluation of the coronary arteries, as well as the presence of a pericardial effusion or ventricular dysfunction.

110. How do the rates of Kawasaki disease vary between Japan and the United States?

The reported incidence rates of Kawasaki disease in Japan were 243 and 265 per 100,000 in children <5 years of age in 2011 and 2012, respectively. In contrast, the incidence of Kawasaki disease in the United States is between 18 and 21 per 100,000 children <5 years of age. Kawasaki disease rates in the United States are highest among Japanese American children.

Lin MT, Wu MH. The global epidemiology of Kawasaki disease: review and future perspectives. *Glob Cardiol Sci Pract.* 2017(3):e201720.

111. What are the long-term cardiac manifestations of acute rheumatic fever compared with Kawasaki disease?

The most common sequalae of *acute rheumatic fever* include chronic mitral insufficiency often leading to mitral stenosis and aortic insufficiency. These conditions rarely become severe enough to warrant valve replacement in childhood, but are a common cause of chronic mitral and aortic disease in in adults. Children with *Kawasaki disease* may develop aneurysms of the coronary artery. The majority of small aneurysms will resolve; however, larger aneurysms require long-term follow-up and, depending on their size, may require anticoagulation.

112. What are the cardiac manifestations of Takayasu arteritis?

Takayasu arteritis is a chronic inflammatory process that affects the major arteries and can lead to dilatation, dissection, and occlusion of major vessels, thus deriving its other common name: "pulseless disease." Aortic dissection may lead to narrowing or occlusion of the aorta or one of its major branches. Occlusion of the brachial arteries leads to decreased pulses in the arms. Narrowing in the descending aorta leads to coarctation of the aorta. Damage to the renal arteries results in renovascular hypertension. Treatment is directed at control of the inflammatory process, and some patients may require endovascular intervention or surgery, depending on the severity of the disease.

PHARMACOLOGY

113. How long before oral digoxin begins to work?

Oral digoxin reaches peak plasma levels 1 to 2 hours after administration, but a peak hemodynamic effect is not evident until 6 hours after administration (versus 2 to 3 hours for intravenous digoxin).

114. What are the side effects of indomethacin in the neonate?

- Mild but usually transient decreased renal function
- Hyponatremia (rare)
- Platelet dysfunction producing a prolonged bleeding time
- Occult blood loss from the gastrointestinal tract

115. What are the indications for prostaglandin E_1 (PGE$_1$) in the neonate?

PGE$_1$ is indicated in cardiac lesions that depend on a PDA to maintain adequate pulmonary or systemic blood flow or to promote adequate mixing.

- Inadequate pulmonary blood flow (e.g., pulmonary atresia with intact ventricular septum, tricuspid atresia with intact ventricular septum, critical pulmonary stenosis)
- Inadequate systemic blood flow (e.g., critical coarctation of the aorta, interrupted aortic arch, HLHS)
- Inadequate mixing (e.g., transposition of the great vessels)

116. What are the major side effects of PGE$_1$?

- Apnea
- Fever
- Cutaneous flushing
- Seizures
- Hypotension
- Bradycardia
- Tachycardia

117. How do α, β, and dopaminergic receptors differ?

- *α:* In vascular smooth muscle, these receptors cause vasoconstriction.
- *β_1:* In myocardial smooth muscle, these receptors increase myocardial contractility (inotropic effect), cardiac rate (chronotropic effect), and AV conduction (dromotropic effect).
- *β_2:* In vascular smooth muscle, these receptors cause vasodilation.
- *Dopaminergic:* In renal and mesenteric vascular smooth muscle, these receptors cause vasodilation.

118. How do relative receptor effects differ by drug type?

See Table 3.6.

Table 3.6 Relative Receptor Effects by Drug Type

DRUG	α	β_1	β_2	DOPAMINERGIC
Epinephrine	+++	+++	+++	0
Norepinephrine	+++	+++	+	0
Isoproterenol	0	+++	+++	0
Dopamine*	0 to +++ (dose related)	++ to +++ (dose related)	++ (dose related)	+++
Dobutamine	0 to +	+++	+	0

Effect of medication: 0 = none; + = small; ++ = moderate; +++ = large.

*For dopamine, at low doses (2 to 5 μg/kg/min), dopaminergic effects predominate. At high doses (5 to 20 μg/kg/min), increased α and β effects are seen. At very high doses (>20 μg/kg/min), a markedly increased α effect with decreased renal and mesenteric blood flow occurs. For dobutamine, β_1 inotropic effects are more pronounced than are chronotropic effects.

119. How are emergency infusions for cardiovascular support prepared?

See Table 3.7.

Table 3.7 Emergency Infusions for Cardiovascular Support

CATECHOLAMINE	MIXTURE	DOSE
Isoproterenol, epinephrine, norepinephrine	0.6 mg × body wt (in kg), added to diluent to make 100 mL	1 mL/hr delivers 0.1 μg/kg/min
Dopamine, dobutamine	6 mg × body wt (in kg), added to diluent to make 100 mL	1 mL/hr delivers 1 μg/kg/min

PHYSICAL EXAMINATION

120. What causes the first heart sound?

The *first heart sound* is caused by the closure of the mitral and tricuspid valves.

121. What causes the second heart sound?

The *second heart sound* is caused by the closure of the aortic and pulmonary valves.

122. In what settings can an abnormal second heart sound be auscultated?

Widely split S_2

- Prolonged RV ejection time
- RV volume overload: ASD, partial anomalous pulmonary venous return
- RV conduction delay: Right bundle branch block

Single S_2

- Presence of only one semilunar valve: Aortic or pulmonary atresia, truncus arteriosus
- P_2 not audible: Tetralogy of Fallot, transposition of great arteries
- A_2 delayed: Severe aortic stenosis
- May be normal in a newborn

Paradoxically split S_2 (A_2 follows P_2)

- Severe aortic stenosis
- Left bundle branch block

Loud P_2

- Pulmonary hypertension

123. What is the difference between pulsus alternans and pulsus paradoxus?

- *Pulsus alternans* is a pulse pattern in which there is alternating (beat-to-beat) variability of pulse strength due to decreased ventricular performance. This is sometimes seen in patients with severe CHF.
- *Pulsus paradoxus* indicates an exaggeration of the normal reduction of systolic blood pressure during inspiration. Associated conditions include cardiac tamponade (e.g., effusion, constrictive pericarditis), severe respiratory illness (e.g., asthma, pneumonia), and myocardial disease that affects wall compliance (e.g., endocardial fibroelastosis, amyloidosis).

124. How is pulsus paradoxus measured?

To measure a pulsus paradoxus, determine the systolic pressure by noting the first audible Korotkoff sound. Then retake the blood pressure by raising the manometer pressure to at least 25 mm Hg higher than the systolic pressure and allow it to fall very slowly. Stop as soon as the first sound is heard. Note that the sound disappears during inspiration. Lower the pressure slowly, and note when all pulsed beats are heard. The difference between these two pressures is the pulsus paradoxus. Normally, in children, there is an 8– to 10–mm Hg fluctuation in systolic pressure with different phases of respiration.

125. What is the differential diagnosis for a systolic murmur in each auscultatory area?

See Fig. 3.12.

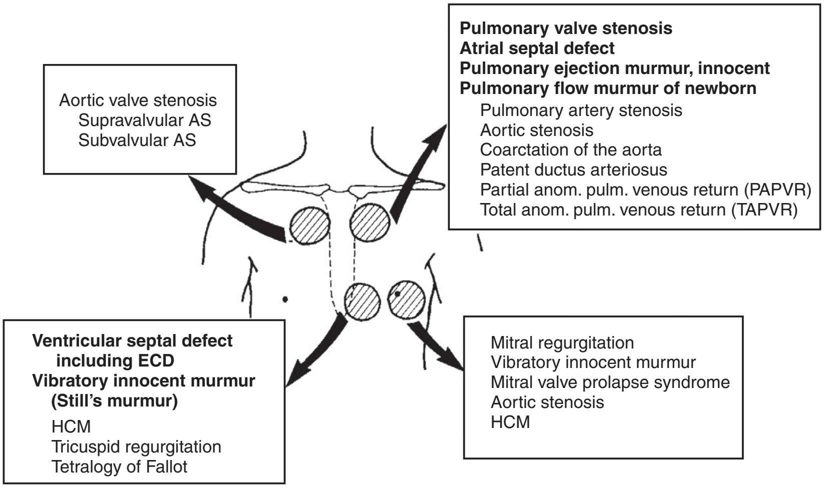
Aortic valve stenosis
Supravalvular AS
Subvalvular AS
Pulmonary valve stenosis
Atrial septal defect
Pulmonary ejection murmur, innocent
Pulmonary flow murmur of newborn
Pulmonary artery stenosis
Aortic stenosis
Coarctation of the aorta
Patent ductus arteriosus
Partial anom. pulm. venous return (PAPVR)
Total anom. pulm. venous return (TAPVR)
Ventricular septal defect including ECD
Vibratory innocent murmur (Still's murmur)
HCM
Tricuspid regurgitation
Tetralogy of Fallot
Mitral regurgitation
Vibratory innocent murmur
Mitral valve prolapse syndrome
Aortic stenosis
HCM

Fig. 3.12 Systolic murmurs audible at various locations. Many may radiate to other areas. Less common conditions are shown in smaller type. *AS*, Aortic stenosis; *ECD*, endocardial cushion defect. *HCM*, hypertrophic cardiomyopathy. (From Park MK. *Pediatric Cardiology for Practitioners.* 4th ed. St. Louis, MO: Mosby; 2002:32.)

126. What are the most common innocent murmurs?

See Table 3.8.

Table 3.8 Most Common Innocent Murmurs

TYPE (TIMING)	DESCRIPTION OF MURMUR	COMMON AGE GROUP
Classic vibratory murmur; Still's murmur (systolic)	Maximal at MLSB or between LLSB and apex Low-frequency vibratory, "twanging string," or musical Grade 2-3/6 in intensity	3-6 years old; occasionally in infancy
Pulmonary ejection murmur (systolic)	Maximal at ULSB Early to midsystolic Grade 1-2/6 in intensity	8-14 years old
Pulmonary flow murmur of newborn (systolic)	Maximal at ULSB Transmits well to left and right chest, axillae, and back Grade 1-2/6 intensity	Premature and full-term newborns; usually disappears by 3-6 months of age
Venous hum (continuous)	Maximal at right (or left) supraclavicular and infraclavicular areas Inaudible in supine position Intensity changes with rotation of head and compression of jugular vein Grade 1-2/6 in intensity	3-6 years old
Carotid bruit (systolic)	Right supraclavicular area and over carotids	Any age
	Occasional thrill over a carotid artery	
	Grade 2-3/6 intensity	

LLSB, Lower-left sternal border; *MLSB,* mid-left sternal border; *ULSB,* upper-left sternal border.

127. What is the effect of sitting up on the typical innocent murmur?

Sitting up usually brings out or increases the intensity of the murmur of a venous hum. In contrast, the typical vibratory innocent murmur along the lower left sternal border is loudest in the supine child and will diminish in intensity and sometimes disappear while sitting upright.

128. What features are suggestive of a pathologic murmur?

- Diastolic murmurs
- Late systolic murmurs
- Pansystolic murmurs
- Continuous murmurs
- Murmurs associated with a thrill
- Murmurs at the aortic area (right-upper sternal border) and tricuspid area (left-lower sternal border)
- Harsh quality
- Associated cardiac abnormalities (e.g., asymmetrical pulses, clicks, abnormal splitting)

McCrindle BW, Shaffer KM, Kan JS, et al. Cardinal clinical signs in the differentiation of heart murmurs in children. *Arch Pediatr Adolesc Med.* 1996;150(2):169–174.

Rosenthal A. How to distinguish between innocent and pathologic murmurs in childhood. *Pediatr Clin North Am.* 1984;31(6):1229–1240.

129. If a murmur is detected, what other factors suggest that the murmur is pathologic?

- **Evidence of growth restriction** (most commonly seen in murmurs with large left-to-right shunts)
- **Associated dysmorphic features** (e.g., valvular disease in Hurler syndrome, Noonan syndrome)
- **Exertional cyanosis, pallor, or dyspnea**, especially if associated with minor exertion such as climbing a few stairs (may be a sign of early CHF)
- **Short feeding times and small volumes** in infants (may be a sign of early CHF)
- **Syncopal or presyncopal episodes** (may be seen in hypertrophic cardiomyopathy)
- **History of intravenous drug abuse** (risk factor for endocarditis)

- **Maternal history of diabetes mellitus** (associated with asymmetrical septal hypertrophy, VSD, D-transposition), **alcohol use** (associated with pulmonic stenosis and VSD), or **other medications**
- **Family history** of CHD

Etoom Y, Ratnapalan S. Evaluation of children with heart murmurs. *Clin Pediatr.* 2014;53(2):111–117.

130. Match the diastolic murmurs with the site where it is typically heard the loudest

1. *Aortic Insufficiency*	A. *Right Upper Sternal Border*
2. *Pulmonary Insufficiency*	B. *Left Midsternal Border*
3. *Mitral Stenosis*	C. *Left Lower Sternal Border*
4. *Tricuspid Stenosis*	D. *Apex*

- *Aortic insufficiency* (A, but also B and D) may be heard along an imaginary line from the right upper sternal border to the apex. It is commonly loudest at the right upper sternal border, but often can be heard loudly at the left mid-sternal border and radiate along an imaginary line from the right upper sternal border to the apex.
- *Pulmonary insufficiency* (B) is typically the loudest at the left middle sternal border.
- *Mitral stenosis* (D) is typically the loudest at the cardiac apex and is often very localized with limited radiation.
- *Tricuspid stenosis* (C) is typically loudest at the left lower sternal border.

KEY POINTS: PATHOLOGIC MURMURS

1. Diastolic
2. Pansystolic
3. Late systolic
4. Continuous
5. Thrill present on examination
6. Additional cardiac abnormalities (e.g., clicks, abnormal splitting, asymmetric pulses)

SURGERY

131. What are shunt operations?

Arterial shunts are connections between a systemic artery and the pulmonary artery and are used to improve oxygen saturation in patients with cyanotic CHD and diminished pulmonary blood flow. *VA shunts* connect a systemic vein and the pulmonary artery and are also used for similar purposes.

132. What are the major shunt operations (Fig. 3.13) for CHD?

- The **Blalock-Taussig (BT)** shunt consists of an anastomosis between a subclavian artery and the ipsilateral pulmonary artery. The subclavian artery can be divided and the distal end anastomosed to the pulmonary

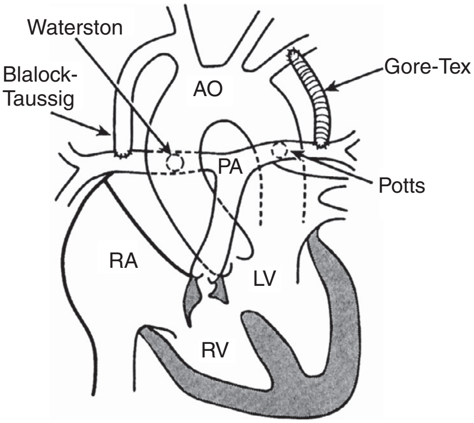

Fig. 3.13 Major shunt operations. *AO,* Aorta; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle. (From Park MK. *Pediatric Cardiology for Practitioners.* 4th ed. St. Louis, MO: Mosby; 2002:194.)

artery (classic BT shunt), or a prosthetic graft (Gore-Tex) can be interposed between the two arteries (modified BT shunt). It allows for pulmonary blood flow in children with severe pulmonary stenosis or atresia.

- The **Sano** shunt (not pictured) is a conduit from the right ventricle to the pulmonary artery and is often used as an alternative to the BT shunt in the Norwood procedure for HLHS.
- The **Waterston** shunt is an anastomosis between the ascending aorta and the right pulmonary artery. This procedure is rarely performed today.
- The **Potts** shunt is an anastomosis between the descending aorta and the left pulmonary artery. This procedure is rarely performed today.

133. What is the purpose of the Fontan procedure?

The *Fontan procedure* (or operation) is designed to reroute systemic venous blood from the superior and inferior vena cava directly to the pulmonary arteries, thus bypassing the right ventricle. It is most commonly used for any cardiac lesion with a single functional ventricle. A common current approach is anastomosis of the superior vena cava (SVC) to the right pulmonary artery and redirection of flow from the inferior vena cava to the right pulmonary artery through either an intracardiac baffle or an extracardiac conduit. This deoxygenated blood flows passively to the lungs and returns to the ventricle to be pumped to the systemic circulation.

Tsai W, Klein BL. The postoperative cardiac patient. *Clin Pediatr Emerg Med.* 2005;6:216–221.

134. What are the most common rhythm disturbances after the Fontan procedure?

Because of the extensive atrial surgery in the Fontan procedure, there are two major cardiac rhythm issues:

- **Loss of sinus rhythm** with either a nonsinus atrial rhythm or junctional rhythm. Atrial pacing may be required in these patients to either increase heart rate or restore AV synchrony.
- **Intra-atrial reentrant tachycardia** was more common after the old-style Fontan procedure because of the incisional scars and size of the atrium. Although less common with the newer surgical techniques, it remains a major clinical problem in these patients; it is often drug resistant and requires either catheter or surgical ablation.

135. How does jugular vein pressure differ in a child with normal cardiac anatomy compared with a child with a Fontan circulation?

In a child with normal intracardiac anatomy, the jugular vein drains to the SVC, which connects to the right atrium. Jugular vein pressure thus reflects pressure in the right atrium and right ventricle during diastole. Normal right ventricular end-diastolic pressure is 2 to 4 mm Hg. In contrast, in a child with a Fontan circulation after surgery, the SVC is surgically connected to the pulmonary artery. Thus the jugular vein reflects pulmonary artery pressure. It is typically 12 to 15 mm Hg in a child with Fontan circulation and can often be higher in a child with failing Fontan circulation.

136. What type of cardiac surgery is associated with the complication of protein-losing enteropathy?

Fontan procedure. Protein-losing enteropathy, which occurs in 2% to 10% of cases, is a condition manifested by variable degrees of ascites, peripheral edema, diarrhea, malabsorption of fat, and hypoalbuminemia. The cardiac function is often normal in these patients, and the cause is attributed to abnormal flow dynamics in the mesenteric vasculature secondary to high pressures in the Fontan circulation.

137. What are some of the reasons to surgically close a VSD?

- Chronic respiratory failure secondary to heart failure
- Chronic heart failure
- Prevention of pulmonary vascular obstructive disease
- Growth failure secondary to chronic heart failure
- Persistent left heart volume load with chronic cardiomegaly
- Aortic valve prolapse with aortic valve insufficiency
- Recurrent endocarditis

138. What are the indications for closure of an ASD?

Asymptomatic children with a secundum ASD associated with RV dilation and increased pulmonary blood flow typically undergo elective closure between 3 and 5 years of age to prevent pulmonary hypertension and arrhythmias associated with chronic cardiomegaly. Children with a typical secundum ASD can usually be closed with catheterization techniques; large secundum defects or associated lesions are typically closed at surgery. A primum or sinus venosus ASD is closed with surgery. The rare infant with a symptomatic ASD should undergo surgery at the time of diagnosis.

139. What is the typical timing for the three operations for children with HLHS?

HLHS is characterized by a severely underdeveloped left ventricle with small and/or poorly formed mitral and aortic valves and portions of the ascending aorta. The defects do not support the systemic circulation.

The condition is fatal if untreated. Staged palliative surgery is one approach for families who choose intervention over comfort measures.

- **Newborn**: *Norwood procedure*—reconstruction of the new aorta, atrial septectomy, and pulmonary shunt
- **4 to 8 months**: *Glenn shunt* (hemi-Fontan)—superior caval to pulmonary artery connection
- **2 to 4 years**: *Fontan procedure*—inferior vena cava to pulmonary artery connection

140. What are long-term survival rates for children who undergo surgery for HLHS?

Before the advances of the Norwood procedure in the 1980s, children with HLHS invariably died in the first weeks of life. After the introduction of the Norwood procedure, survival rates have steadily increased. In the multicenter randomized Single Ventricle Reconstruction (SVR) trial of infants with HLHS, 3-year survival was 64% for Norwood procedure with a right ventricle–to–pulmonary artery shunt (Sano) versus 59% for infants with Norwood procedure with a modified BT shunt. By 6 years of age, approximately 15% of patients in both groups had developed heart failure. One in five patients had had a thrombotic event, and one in six had had seizures.

Mahle WT, Hu C, Trachtenberg F, et al. Heart failure after the Norwood procedure: an analysis of the Single Ventricle Reconstruction Trial. *J Heart Lung Transplant.* 2018;37(7):879–885.

Newburger JW, Sleeper LA, Gaynor JW, et al. Transplant-free survival and interventions at 6 years in the SVR trial. *Circulation.* 2018; 137(21):2246–2253.

141. What is the long-term prognosis for heart transplantation during infancy and childhood?

Survival statistics have improved dramatically with the use of newer and safer immunosuppressive agents. However, children who receive transplanted hearts are at increased risk for cardiac rejection, infection, accelerated coronary artery disease, and lymphoproliferative syndromes. Recent estimated 5-year survival rates vary between 65% and 80%.

142. A 5-year-old girl, 2 weeks after an uncomplicated repair of a secundum ASD, presents with fever, respiratory distress, and a history sitting up while sleeping since discharge. What is the immediate concern?

Postpericardiotomy syndrome (PPCS) and **pericardial effusion.** PPCS typically occurs between 7 and 21 days after any surgical procedure that opens the pericardial space. Symptoms may include fever, chest pain, irritability, dyspnea, and a preference for sitting up. Physical examination may show fever, tachycardia, increased respiratory rate, hypotension with decreased pulse pressure, muffled heart tones, distended neck veins, hepatomegaly, and pulsus paradoxus. The differential diagnosis includes residual cardiac lesions, cardiomyopathy, pneumonia, sepsis, and pleural effusions.

143. What is the etiology of postoperative hypertension after repair of coarctation of the aorta?

Postoperative hypertension is believed to be due to baroreceptor trauma secondary to surgery, an increase in circulating catecholamines, and an exaggerated renin–angiotensin system response. Treatment with sedation, analgesia, esmolol, nitroprusside, and propranolol has been successful. These drugs can be changed to enalapril or captopril when oral feedings are resumed.

144. A 5-year-old boy, 6 days after an uncomplicated surgical repair of a coarctation of the aorta, presents with respiratory distress; a left pleural effusion is noted on a chest x-ray. What is the likely appearance and composition of the pleural fluid?

The pleural fluid is turbid, milky-white, high in triglycerides and lymphocytes, and is consistent with a **chylothorax**. After surgical repair of a coarctation of the aorta, PDA, or a vascular ring, patients are at risk for chylous pleural effusions secondary to trauma to the thoracic duct. Injury to the thoracic duct can result in leakage of lymphatic/chylous fluid (of intestinal origin) into the pleural space. This typically starts after feedings are resumed and the patient starts to increase fat intake, which increases chyle formation. Children usually respond to a nonfat diet or a diet enriched for medium-chain triglycerides, but sometimes will need surgical ligation of the thoracic duct.

Acknowledgment

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CHAPTER 4

DERMATOLOGY

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ACNE

1. When is acne most likely to develop?

The development of microcomedones is typically the earliest sign of acne. Studies have shown that comedones occur in three-fourths of premenarchal girls at an average age of 10 years and in about half of 10- to 11-year-old boys. They may herald (or predate) the onset of puberty.

2. When are pimples precocious?

Acne vulgaris that begins <**7 years** warrants further investigation for endocrine abnormalities such as androgen excess or precocious puberty.

Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics.* 2013;131(Suppl 3):S163–S185.

3. A 6-year-old girl presents for evaluation of acne. What additional signs are worrisome for central precocious puberty and need prompt referral to an endocrinologist?

In both sexes, **crossing linear growth percentiles** is an important indicator of pathology. Progressive breast development before 8 years in girls and penile and/or testicular enlargement before 9 years in boys are important signs. Isolated axillary or pubic hair (premature adrenarche) with normal linear growth is less indicative of pathology.

Kaplowitz P, Bloch C. Evaluation and referral of children with signs of early puberty. *Pediatrics.* 2016;137(1):e20153732,

4. Which skin structure is involved in acne pathogenesis?

Pilosebaceous unit. It consists of a vellus hair follicle in association with sebaceous glands, which secrete sebum into the lumen of the follicle.

5. What are the four key factors involved in acne pathogenesis?

- Androgen-dependent sebum production
- Abnormal follicular keratinization, which leads to follicular plugging
- Proliferation of *Propionibacterium acnes* bacteria that live in the lumen of the follicle and thrive in an anaerobic environment; *P. acnes* is lipolytic and breaks down sebum, releasing mediators of inflammation
- Inflammation

6. What is the difference between neonatal acne and infantile acne?

- *Neonatal or "baby" acne* occurs in up to 20% of newborns and typically presents during the first 4 weeks after birth. Erythematous papulopustules develop on the face, especially the cheeks. It has been attributed to the transient elevation of androgenic hormones (both maternally derived and endogenous) that are present in a newborn infant. The lesions typically resolve within 1 to 3 months as androgen levels fall. *Neonatal cephalic pustulosis* is a term that has been proposed to replace *neonatal acne.* Because lesions have been shown to contain *Malassezia* species, neonatal "acne" may actually represent an inflammatory reaction to this yeast flora and not true acne at all.
- *Infantile acne* is uncommon and usually presents on a delayed basis (3 to 6 months). Histologically, the lesions are similar to true acne vulgaris as seen in older children: open and closed comedones, inflammatory papules, and, rarely, nodules may be present. An examination for signs of androgen excess is indicated, although most patients with this condition have no evidence of precocious puberty or increased hormonal levels. Systemic therapy may be required to minimize scarring.

7. Which disorders resemble neonatal and infantile acne?

- **Miliaria rubra** or **pustulosa**, often in areas of occlusion and skin folds
- **Milia**, white papules without surrounding erythema
- **Sebaceous hyperplasia**, yellowish papules typically on the nose
- **Seborrheic dermatitis**, erythematous scaly patches rather than pustules

8. Which medications may exacerbate acne?

Anabolic steroids and corticosteroids, lithium, barbiturates, and progesterone-only contraceptives.

KEY POINTS: MAIN FACTORS IN ACNE PATHOGENESIS

1. Androgen-dependent sebum production
2. Abnormal follicular keratinization
3. Proliferation of *P. acnes*
4. Inflammation

9. In addition to acne, what other historical and physical examination findings should prompt further evaluation for the possibility of polycystic ovary syndrome?

Although menstrual irregularities are expected in the first year after menarche, occurrence in conjunction with acne and hirsutism (excess facial and body hair) should prompt further evaluation.

10. What is the therapeutic approach to acne?

Acne therapies, including comedolytics, antibacterial agents, and hormonal modulators, target various factors involved in acne pathogenesis.

- **Topical antimicrobials** including benzoyl peroxide (BPO), erythromycin, and clindamycin may be used to decrease *P. acnes*. If erythromycin or clindamycin is used, it should be combined with BPO to decrease the risk for *P. acnes* antibiotic resistance. BPO itself is bactericidal against *P. acnes*.
- **Topical retinoids** tretinoin, tazarotene (Pregnancy Category X), and adapalene are comedolytic agents that prevent the formation of new keratin plugs.
- **Systemic antibiotics** (e.g., tetracycline and its derivatives) are most frequently used for moderate to severe papulopustular acne.
- **Systemic retinoids** (isotretinoin) are used in cases of severe acne vulgaris. The exact mechanism of action of isotretinoin is not known, but it affects all four factors in acne pathogenesis: keratinization/follicular plugging, inhibition of sebaceous gland activity, reduced *P. acnes,* and inflammation.
- **Hormonal modulation** is most commonly accomplished with oral contraceptives. Select oral contraceptives are approved by the Food and Drug Administration (FDA) to treat moderate to severe acne in menstruating females >14 years. Antiandrogenic agents such as spironolactone have been used in some teenage females with premenstrual flares, hirsutism, and male-pattern alopecia.

Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics.* 2013;131(Suppl 3):S163–S185.

11. When is the best time to apply tretinoin?

Tretinoin is inactivated by sunlight, so it is recommended to apply it in the **evening**. BPO may be used by the patient the next morning.

12. Which combination of acne products will cause a yellow-orange skin discoloration?

The use of **topical dapsone** 5% gel (off-label for patients <12 years) plus BPO will lead to a yellow-orange skin discoloration. Patients should be warned to avoid applying these medications at the same time. **Topical sulfacetamide** applied at the same time as **BPO** will also cause this reaction. If alternating application morning and night, a gentle cleansing should occur between each step. Once the reaction occurs, it may take from a few days up to 2 months to resolve.

Dubina MI, Fleischer AB Jr. Interaction of topical sulfacetamide and topical dapsone with benzoyl peroxide. *Arch Dermatol.* 2009;145(9):1027–1029.

13. What other topical acne products should not be used in combination?

The combination of topical tretinoin plus BPO applied at the same time is known to cause oxidation and inactivity of the tretinoin. Adapalene (Differin), now available over the counter, also works on the retinoid receptors and should not be mixed with BPO. However, there is a prescription topical combination product (Epiduo or adapalene–benzoyl peroxide) that contains adapalene in a stable combination with 2.5% BPO. It is FDA-approved to treat acne in patients who are ≥9 years of age.

Dubina MI, Fleischer AB Jr. Interaction of topical sulfacetamide and topical dapsone with benzoyl peroxide. *Arch Dermatol.* 2009;145(9):1027–1029.

14. Which nonpharmacologic factors are important in the control of acne?

- Avoid vigorous scrubbing or picking of lesions
- Choose noncomedogenic makeup or other facial products
- Studies are evaluating the influence of a high-glycemic-index diet and insulin resistance

15. A teenager with acne presents for evaluation of recurrent superficial, crusted facial erosions without previous prescription treatment and a negative skin culture. What common over-the-counter (OTC) acne product(s) should be considered as causative?

BPO and **salicylic acid** can both cause irritation and, rarely, allergic contact dermatitis. BPO is an excellent OTC starting point to treat teenage acne, as it is bactericidal for *P. acnes* and generally well tolerated. Salicylic acid (1% to 2%) is an OTC keratolytic agent that is useful to control blackheads and whiteheads. It is recommended to apply any new product on a small area of skin for 3 days before applying it more broadly as labeled.

Kim C, Craiglow BG, Watsky KL, et al. Allergic contact dermatitis to benzoyl peroxide resembling impetigo. *Pediatr Dermatol.* 2015;32(4):e161–e162.

16. What serious side effects may be associated with systemic minocycline therapy for acne?

Tetracyclines, including the derivative minocycline, are widely prescribed oral antibiotics for acne and have been used safely over long periods. They are contraindicated for patients <8 years because of the potential for permanent dental staining. Rare reactions—particularly to minocycline—have included skin discoloration, pneumonitis, autoimmune hepatitis, drug-induced lupus, serum sickness–like reactions, and severe hypersensitivity reactions.

Brown RJ, Rother KI, Artman H, et al. Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. *Arch Dermatol.* 2009;145(1):63–66.

17. When is the use of oral isotretinoin indicated in teenagers with acne?

Isotretinoin, which is 13-cis-retinoic acid, is most appropriately used for **nodulocystic acne**, **acne conglobata**, or **scarring acne** that has been unresponsive to standard modes of treatment (e.g., oral/topical antibiotics, topical retinoids). Given the known side effect of teratogenicity if even one dose of isotretinoin is taken during pregnancy or if a female becomes pregnant within 30 days of the last dose, rigorous monitoring and definitive contraceptive counseling are mandatory. The FDA and the manufacturers of isotretinoin created a registry, called iPLEDGE (www.ipledgeprogram.com), in an effort to reduce the risk for fetal exposure to isotretinoin. This program monitors patients on isotretinoin with monthly laboratory tests and verification of contraception and knowledge of risks.

Costa CS, Bagatin E, et al. Oral isotretinoin for acne. *Cochrane Database Syst Rev.* 2018;11:CD009435.
Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics.* 2013;131(Suppl 3):S163–S185.
Merritt B, Burkhart CN, Morrell DS. Use of isotretinoin for acne vulgaris. *Pediatr Ann.* 2009;38(6):311–320.

CLINICAL ISSUES

18. How are common skin lesions defined?

Morphologic descriptions of primary cutaneous lesions are as follows:

- **Macule**: a circumscribed, flat area, recognizable by color variation from surrounding skin, ≤1 cm
- **Patch**: a flat area recognizable by color variation from surrounding skin, >1 cm
- **Papule**: a circumscribed elevation, ≤1 cm
- **Plaque**: a large superficial circumscribed elevation, >1 cm
- **Nodule**: a circumscribed solid elevation, ≥1 cm
- **Vesicle** (small blister): a clear, fluid-filled elevation, ≤1 cm
- **Bulla** (large blister): a fluid-filled elevation, >1 cm
- **Pustule**: a circumscribed elevation of skin filled with pus

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19. When might a dermoid cyst be more than just a dermatologic problem?

Dermoid cysts are congenital anomalies present at birth and caused by entrapment of cutaneous tissues (e.g., sweat and sebaceous glands, hair follicles) along embryonal fusion lines. They may grow slowly and not be noticed for months or years. Dermoids are commonly located on the face and scalp, but can occur anywhere on the skin (Fig. 4.1). The most common location is the lateral eyebrow. However, be wary of **midline facial dermoid cysts**, as they carry a risk for intracranial connection. This can result in meningitis if there is rupture of the cyst contents into the central nervous system (CNS).

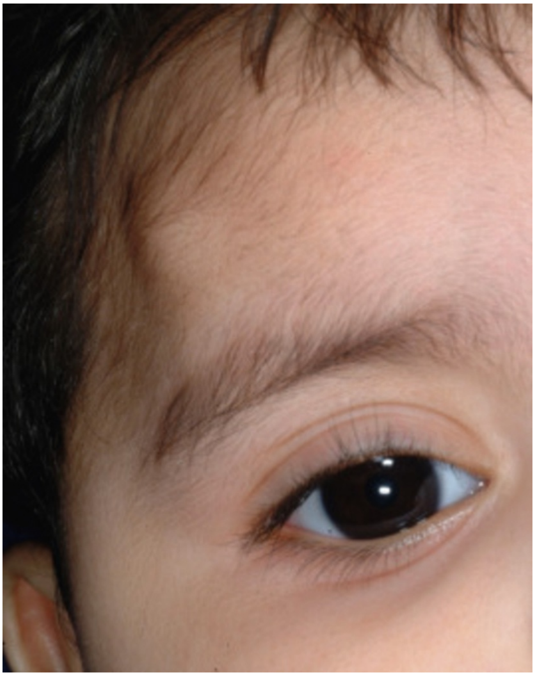

Fig. 4.1 Dermoid cyst in a 5-month-old. The lateral midforehead distribution is slightly higher than most dermoid cysts, which typically present in the lateral eyebrow region. The nodule was subcutaneous, mobile, and nontender. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*. 5th ed. Philadelphia, PA: Elsevier; 2016:27.)

20. What skin findings in the midline lumbosacral region can be associated with occult spinal dysraphism?

Skin findings in the lumbosacral area can be associated with occult spinal dysraphism. Some markers are considered higher risk for dysraphism than others. Prospective studies are lacking to quantify the risk for each type of skin finding. Higher-risk findings include:

- Aplasia cutis congenita
- Appendages (skin tags, tail)
- Dermoid cysts and sinus tracts
- Lipoma
- Hypertrichosis
- Pits: Sinuses or large dermal dimples ($>$0.5 cm) that are located $>$2.5 cm from the anal verge (particularly with lateral deviation of the cleft)
- Vascular lesions (hemangioma—Fig. 4.2—greater risk than isolated port wine stain or telangiectasias)
- Pigmentation variants (both hyperpigmentation, including lentigo and melanocytic nevus, and hypopigmentation)
- The presence of two or more midline markers increases the risk for dysraphism

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Sewell MJ, Chiu YE, Drolet BA. Neural tube dysraphism: review of cutaneous markers and imaging. *Pediatr Dermatol.* 2015; 32(2):161–170.

Drolet BA, Chamlin SL, Garzon MC, et al. Prospective study of spinal anomalies in children with infantile hemangiomas of the lumbosacral skin. *J Pediatr.* 2010;157(5):789–794.

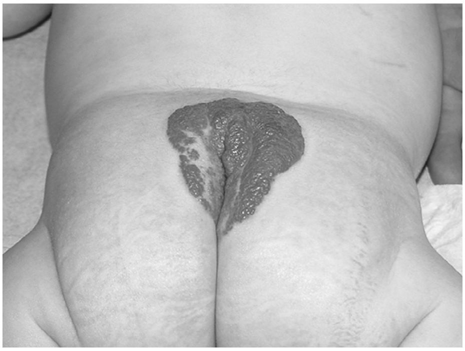

Fig. 4.2 Lumbosacral hemangioma with underlying tethered cord. (From Drolet BA, Garzon MC, eds. *Birthmarks of medical significance. Pediatr Clin North Am.* 2010;57:1077.)

KEY POINTS: MIDLINE LUMBOSACRAL LESIONS ASSOCIATED WITH OCCULT SPINAL DYSRAPHISM OR TETHERED CORD

1. Aplasia cutis congenita
2. Sacral pits (particularly with lateral deviation of the gluteal cleft or atypical morphology)
3. Hairy patches
4. Appendages (skin tag or tail)
5. Dermoid cyst or sinus tract
6. Lipoma
7. Vascular lesions (hemangioma, port wine stain)
8. Pigmentation variants (hyperpigmentation, including lentigo and melanocytic nevus, and hypopigmentation)
9. Two or more skin findings occurring together increase the risk for dysraphism

21. What is the significance of accessory tragi?

Accessory tragi are fleshy papules or nodules that are typically anterior to the normal tragus or, less commonly, on the cheek or jawline. They contain variable amounts of cartilage. In most cases, accessory tragi are isolated cutaneous findings. Extensive defects may be associated with hearing loss. Newborns with accessory tragi should have their hearing tested. Less commonly, they are associated with other first branchial arch abnormalities (e.g., cleft lip and palate) or rare syndromes such as Treacher Collins, VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities), or oculoauriculovertebral syndrome. Accessory tragi are treated by surgically excising the papule and its cartilaginous stalk.

22. What is a common cause of a midline neck mass in a young child?

Thyroglossal duct cysts are the most common type of congenital cysts in the neck (Fig. 4.3). They are often not visible at birth and commonly present as a swollen midline upper neck mass after a respiratory tract infection. The mass elevates with protrusion of the tongue. Treatment is surgical excision. Patients with suspected thyroglossal duct cysts need to have their thyroid function assessed before surgery because ectopic thyroid tissue can commonly occur.

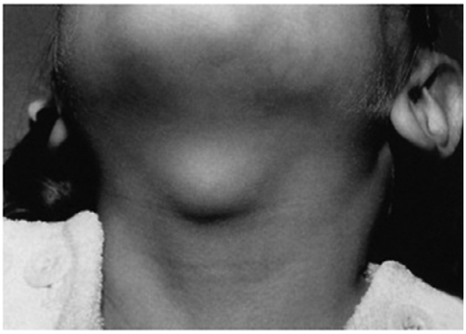

Fig. 4.3 Thyroglossal duct cyst, as typically seen in the midline of the neck at or near the hyoid bone. (From Flint PW, Haughey BH, Lund VC, et al, eds. *Cummings Otolaryngology*. 6th ed. Philadelphia, PA: Saunders; 2015:3058.)

23. What conditions cause ringlike rashes on the skin?

Not all rings are ringworm. Annular (ringlike) skin lesions can be seen in a wide variety of skin diseases in children. Common causes of these lesions include the following:

- Tinea corporis (ringworm)
- Dermatitis (especially nummular)
- Psoriasis
- Urticaria
- Granuloma annulare (often composed of small papules without overlying scale)
- Erythema migrans
- Systemic lupus erythematosus

KEY POINTS: DIFFERENTIAL DIAGNOSES OF RINGLIKE SKIN RASHES

1. Tinea corporis
2. Dermatitis (atopic, nummular, or contact)
3. Psoriasis
4. Granuloma annulare (often composed of small papules without overlying scale)
5. Erythema migrans
6. Systemic lupus erythematosus

24. What is the appearance and natural history of molluscum contagiosum?

Molluscum contagiosum is a common skin infection caused by a pox virus. Lesions are small, pinkish-tan, dome-shaped papules that often have a dimpled or umbilicated center (Fig. 4.4). They are usually asymptomatic, but may be associated with an eczematous dermatitis and itch. Superinfection may complicate the course, require antibiotic therapy, and increase the likelihood of scarring after resolution. In healthy children, the course is self-limited but may last for 2 years. In some cases, persistent and widespread molluscum may require screening for congenital or acquired immunodeficiency.

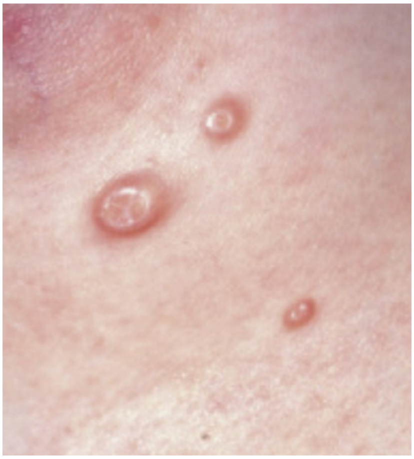

Fig. 4.4 Molluscum contagiosum (thoracic location, below nipple). Note central umbilication. (From James WD, Elston DM, Treat JR, et al, eds. *Andrews' Diseases of the Skin*. 13th ed. Philadelphia, PA: Elsevier; 2020:391.)

25. What is the best way to eradicate molluscum contagiosum?

There is no consensus regarding the "best way" to manage molluscum in healthy children. Treatment can be considered to relieve the discomfort such as itching associated with the infection, decrease the likelihood of continued spreading, limit the transmission to household contacts, prevent secondary infection, and reduce cosmetic concerns. If watchful waiting is not desired, therapeutic options include destructive methods. Curettage (with core removal), cryotherapy, and treatments with agents that create localized irritation or an inflammatory response (e.g., topical retinoids applied sparingly) have been used. A popular method involves the use of a blistering agent, cantharidin, which is applied to individual lesions.

American Academy of Pediatrics. Molluscum contagiosum. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:565–566.
Vakharia PP, Chopra R, Silverberg NB, Silverberg JI. Molluscum contagiosum and warts: a systematic review. *Am J Clin Dermatol.* 2018;19(6):791–803.

26. What infection control measures are appropriate for molluscum contagiosum?

No control measures are required for isolated cases. Restricting direct person-to-person contact and sharing of potentially contaminated fomites, such as towels and bedding, may decrease spread when outbreaks occur. Molluscum contagiosum should not prevent a child from attending child care or school or from swimming in public pools. Covering lesions is not necessary for child care. It has been recommended that when possible and when lesions are not covered by clothing, they should be covered with an appropriate dressing when participating in sports activities.

American Academy of Pediatrics. Molluscum contagiosum. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:565–566.

27. What are the common causes of acute urticaria in children?

Acute urticaria may last for several weeks. If it persists beyond that period, it is typically characterized as chronic urticaria. In children, the most common causes of acute urticaria include the five "I's":

- **I**nfection (viral and bacterial are the most frequent, but fungal pathogens may also cause urticaria)
- **I**nfestation (parasites)
- **I**ngestion (medication and foods)
- **I**njections or infusions (immunizations, blood products, and antibiotics)
- **I**nhalation (allergens such as pollens and molds)

Weston W, Orchard D. Vascular reactions. In Schachner LA, Hansen RC, eds. *Pediatric Dermatology.* 3rd ed. St. Louis, MO: Mosby; 2003:801–831.

KEY POINTS: COMMON CAUSES OF URTICARIA—THE FIVE I'S

1. **I**nfection (viral and bacterial are the most frequent, but fungal pathogens may also cause urticaria)
2. **I**nfestation (parasites)
3. **I**ngestion (medications and foods)
4. **I**njections or infusions (immunizations, blood products, and antibiotics)
5. **I**nhalation (allergens such as pollens and molds)

28. Which diseases may cause a "strawberry tongue"?

Group A beta hemolytic streptococcal infections and **Kawasaki disease** are the most common disorders associated with a strawberry tongue. The "strawberry-like" surface characteristics are caused by prominent lingual papillae.

29. What are secondary cutaneous manifestations of group A streptococcal infections?

Impetigo, ecthyma, and cellulitis are common examples of *primary* cutaneous infections, but it is important to recognize *secondary* or *reactive* skin manifestations that result from immune activation.

- **Scarlet fever rash**, caused by streptococcal pyrogenic exotoxins (erythrogenic toxins) that lead to immune activation, often follows tonsillitis or pharyngitis. It is an erythematous blanchable exanthem on the upper body with a characteristic sandpaper-like texture ("sunburn with goose pimples").
- **Pastia lines** (linear petechial streaks) are seen in the axillary, antecubital, and inguinal areas.
- **Strawberry tongue**: The tongue is initially white with bright red papillae, but later becomes beefy red.
- **Desquamation**: Occurs after 7 to 10 days and can last for 2 to 6 weeks.
- **Erythema nodosum**: Although more common in adults, strep infections account for a number of cases in childhood. Crops of red to blue tender nodules appear most commonly over the anterior shins or other extremities (Fig. 4.5). Erythema nodosum is an inflammatory panniculitis, a disease localized in the subcutaneous fat.

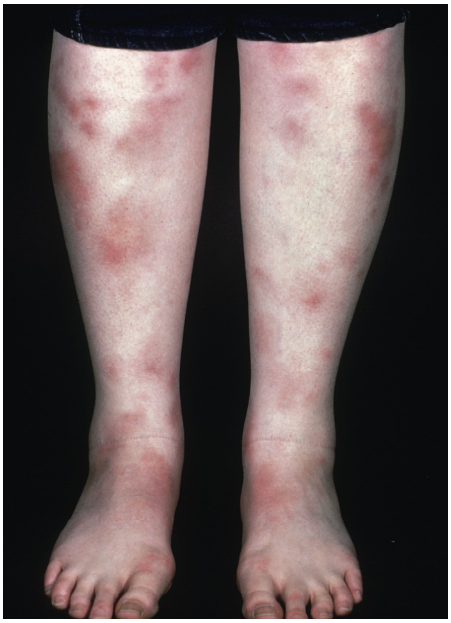

Fig. 4.5 Erythema nodosum with red, tender nodules over the anterior shins and ankles. (From James WD, Elston DM, Treat JR, et al, eds. *Andrews' Diseases of the Skin*. 13th ed. Philadelphia, PA: Elsevier; 2020:486.)

30. What is the characteristic clinical picture of erythema nodosum?

A prodrome of fever, chills, malaise, and arthralgia may precede the typical skin findings. Crops of red to blue tender nodules appear over the anterior shins. Lesions may be seen on the knees, ankles, thighs, and, occasionally, the lower extensor forearms and face. They may evolve through a spectrum of colors that resemble a bruise. Often the changes are misdiagnosed as cellulitis or secondary to a traumatic event. In addition to group A streptococcal infections, this condition is associated with a variety of infectious (e.g., tuberculosis) and noninfectious (e.g., ulcerative colitis, leukemia) causes.

31. What, technically, are warts?

Benign epidermal tumors caused by multiple types of human papillomaviruses.

32. How are plantar warts distinguished clinically from calluses?

Plantar warts are warts on the soles of the feet that can be painful. They are flat or slightly raised areas of firm hyperkeratosis with a collarette of normal skin. Unlike *calluses,* with which they can be confused, plantar warts cause obliteration of the normal skin lines (dermatoglyphics). Pinpoint-sized, dark red dots (thrombosed capillaries) may be seen within the wart (Fig. 4.6). One clinical trick to help distinguish calluses from plantar warts is the *squeeze maneuver.* Pressure applied perpendicularly to a plantar wart typically will not cause pain, but will cause pain in a patient with a callus (due to underlying bone tenderness). Applying pressure to the left and right sides of

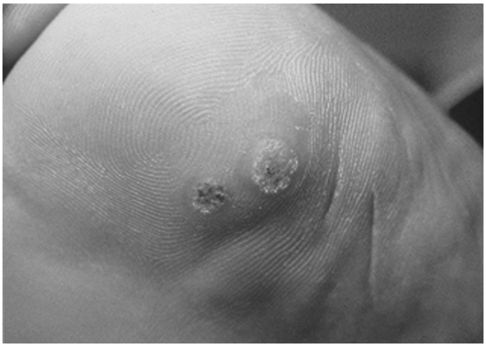

Fig. 4.6 Plantar warts. Note disruption of skin lines. Characteristic black dots in the warts are thrombosed capillaries. (From Cohen BA. *Pediatric Dermatology*. 2nd ed. London: Mosby; 1999:115.)

the lesion at a 45-degree angle by squeezing toward the center (lateral compression) will elicit substantial discomfort in patients with plantar warts but not in patients with calluses.

Zaiac MN, Mlacker S. The squeeze maneuver. *Cutis.* 2016;97(3):202–204.

33. How are common warts treated?

The mode of therapy depends on the type and number of warts, the location on the body, and the age of the patient. No matter what treatment is used, warts can always recur; there are no absolute cures. The major goal is to remove warts without residual scarring. Of course, another option is no treatment at all, because most warts self-resolve, but they may take years to do so. A variety of therapies are used. The most commonly used therapy is salicylic acid with regular paring and occlusion. The second is cryotherapy (topical liquid nitrogen) in combination with salicylic acid. Other therapies, including topical tretinoin, duct tape application, electrodessication, pulsed dye laser, topical imiquimod, and contact immunotherapy, have been used to treat recalcitrant warts in children. In some case reports, oral cimetidine has been reported to be effective, perhaps because of its immunomodulatory activity, although an evidence base is lacking.

Sterling J. Treatment of warts and molluscum: what does the evidence show? *Curr Opin Pediatr.* 2016;28(4):490–499.

Lynch MD, Cliffe J, Morris-Jones R. Management of cutaneous viral warts. *BMJ.* 2014;348:g3339.

34. An 8-year-old has a hard, nontender, freely mobile nodule of the cheek with a slightly bluish hue of the skin. What is the most likely diagnosis?

Pilomatricoma (pilomatrixoma). Also called a *benign calcifying epithelioma of Malherbe,* a pilomatricoma is a benign tumor that often arises in children and adolescents on the face and neck. Calcified lesions often show a “tent” or “teeter totter sign” (pushing down on the edge causes the other end of the growth to bulge). Pilomatricomas are associated with mutations in the β-catenin gene. They are usually not confused with a malignant condition, but excision is often recommended because these nodules increase in size or may become inflamed or infected.

Schwarz Y, Pitaro J, Waissbluth S, Daniel SJ. Review of pediatric head and neck pilomatrixoma. *Int J Pediatr Otorhinolaryngol.* 2016;85:148–153.

35. What are the most common causes of lumps and bumps in the skin of children?

Although most parents fear malignancy, nodules and tumors in the skin are rarely malignant. Congenital cysts such as a thyroglossal duct cyst (see question 22) branchial cleft cyst, or a dermoid cyst (see question 19) are common causes of lumps and bumps in young children. Epidermal inclusion cysts are one of the most common causes in older children and adolescents and are often recognized by their central punctum. Pilomatricomas are another common pediatric cause (see question 34). Deep infantile hemangiomas may develop in early infancy; they are soft masses but may be difficult to recognize if they are not associated with the superficial red component of the hemangioma. Imaging may be indicated if there are no external cutaneous clues. Any rapidly progressive or firm, tender lumps should be evaluated promptly, because a pediatric surgery referral may be required to assist with a definitive diagnosis and to rule out the rare cases of malignancy.

Wyatt AJ, Hansen RC. Pediatric skin tumors. *Pediatr Clin North Am.* 2000;47(4):937–963.

36. Why is a pyogenic granuloma neither pyogenic nor a granuloma?

A *pyogenic granuloma,* also called a *lobular capillary hemangioma,* is a common acquired lesion that develops typically at the site of trauma on any part of the body. Local vascular proliferation occurs, often rapidly, and bleeding may develop (Fig. 4.7). Recently, mutations in the genes *RAS* and *BRAF* have been identified in pyogenic granulomas

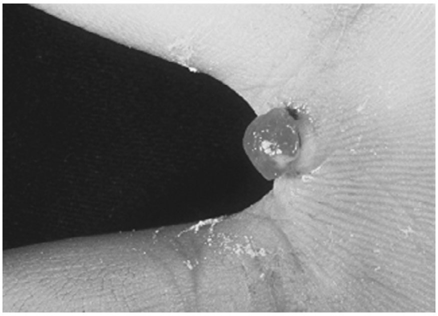

Fig. 4.7 Pyogenic granuloma in the web space between fingers. (From Cohen BA. *Pediatric Dermatology*. 2nd ed. London: Mosby;1999.)

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and are hypothesized to play a role in their development. Curettage and electrodessication of the base are curative. The lesion is neither an infectious pyoderma nor a granuloma on biopsy.

37. What condition is classically diagnosed by the Darier sign?

Mastocytoma. This is a benign lesion composed of mast cells that arises at birth or during early infancy. It appears as a pink/tan plaque or nodule, often with a *peau d'orange* surface. *Darier sign* refers to the eliciting of erythema and an urticarial wheal by stroking or rubbing the lesion. The skin changes are caused by the release of histamine from the mechanically traumatized mast cells.

38. What disorder can present as "freckles" associated with hives?

Urticaria pigmentosa (mastocytosis). Presenting at birth or during early infancy, multiple mastocytomas appear as brown macules, papules, or plaques (vesicle formation can also occur) and are often mistaken for freckles or melanocytic nevi. Lesions are usually only cutaneous, but infrequently they may affect other organ systems (e.g., lungs, kidney, gastrointestinal tract, CNS). The Darier sign is a key feature of diagnosis.

39. What is an SSSI?

SSSI stands for **skin and skin structure infection** (previously known as *SSTI* or *skin and soft tissue infection*). These are a group of infections that include impetigo, folliculitis, furuncles, secondary infections at sites of skin trauma, and cellulitis that are frequently caused by *Staphylococcus aureus.*

40. Is topical or systemic therapy better for impetigo?

Impetigo is an SSSI that can be caused by either *S. aureus* or group A streptococcus. Before starting treatment, it is important to obtain a skin culture, given that methicillin-resistant *S. aureus* (MRSA) has become more common. Treatment usually requires an antibiotic that is active against both streptococci and staphylococci. Topical antibiotics can be used in localized disease. The components of OTC triple-antibiotic ointment (usually bacitracin–neomycin–polymyxin B) do have some activity against the pathogenic bacteria, but mupirocin is more effective as a topical agent (although resistance to mupirocin is on the rise). Systemic antibiotics, with activity against both *S. aureus* and group A streptococcus, are considered for extensive involvement; outbreaks among household contacts, schools, or athletic teams; or if topical therapy has failed.

American Academy of Pediatrics. Staphylococcus aureus. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:733–746.

Breyre A, Frazee BW. Skin and soft tissue infections in the emergency department. *Emerg Clin North Am.* 2018;36(4):723–750.

41. What dermatologic sign starts from a scratch?

Dermographism (dermatographism) occurs when susceptible skin is stroked firmly with a pointed object. The result is a red line that is followed by an erythematous flare, which is followed by a wheal (Fig. 4.8). This "triple response of Lewis" usually occurs within 1 to 3 minutes. Dermographism (or skin writing) is an exaggerated triple response of Lewis and is

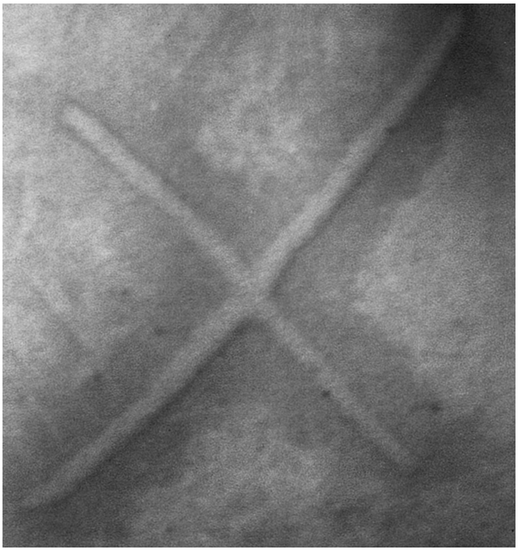

Fig. 4.8 Dermographism. An urticarial response is elicited by firm stroking of the skin. (From Goldbloom RB. *Pediatric Clinical Skills.* 4th ed. Philadelphia, PA: Elsevier Saunders; 2011, color plate 19-8.)

seen in patients with urticaria. The tendency to be dermographic can appear at any age and may last for months to years. The cause is often unknown. White dermographism is seen in patients with an atopic diathesis, in whom the red line is replaced by a white line without a subsequent flare and wheal.

42. Does a geographic tongue occur as a result of global travel?

No, so there is no need to stay home. *Geographic tongue* refers to the benign condition in which denudations of the filiform papillae on the lingual surface occur, giving the tongue the appearance of a relief map (Fig. 4.9). The patterns may change over hours and days, and the histopathology resembles that of psoriasis. The patient is usually asymptomatic. No treatment is effective or necessary because self-resolution is the rule.

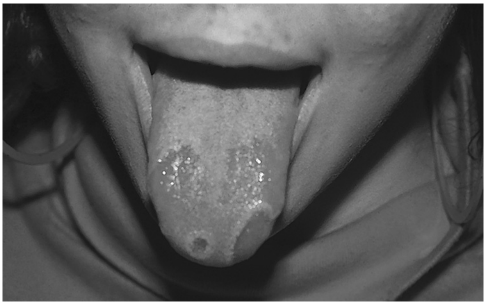

Fig. 4.9 Geographic tongue. (From Sahn EE. *Dermatology Pearls*. Philadelphia, PA: Hanley & Belfus; 1999:162.)

ECZEMATOUS DISORDERS

43. What is the difference between eczema and atopic dermatitis?

The term *eczema* derives from the Greek word *ekzein,* which means to erupt: *ek (ex)* (out) plus *zein* (to boil). To most physicians, eczema is synonymous with atopic dermatitis, a chronic skin disease manifested by intermittent skin eruptions. **Eczema** is primarily a *morphologic term* used to describe an erythematous, scaling, inflammatory eruption with itching, edema, papules, plaques, vesicles, and crusts. There are other "eczematous eruptions" (nummular eczema, allergic contact dermatitis), but "garden variety" eczema is certainly the most common.

Atopic dermatitis is a broader allergic tendency with multiple dermal manifestations that are mostly secondary to pruritus. Atopic dermatitis has been called an "itch that rashes, not a rash that itches." Its manifestations are dry skin, chronic and recurrent dermatitis, low threshold to pruritus, hyperlinear palms, eyelid pleats (Dennie-Morgan folds), pityriasis alba, and keratosis pilaris, among others.

44. What is the usual distribution of rash in atopic dermatitis?

- *Infantile*: Cheeks; chin; trunk; and extensor surfaces of extremities, knees, and elbows
- *Childhood (age 2 to puberty)*: Neck; feet; wrists; and periorbital, antecubital, and popliteal fossae
- *Adult*: Neck, hands, feet, and antecubital and popliteal fossae

KEY POINTS: MAIN FEATURES OF ATOPIC DERMATITIS

1. Extensor surface involvement in infancy
2. Flexural surface involvement in older children
3. Lichenification with chronic scratching
4. Dennie-Morgan folds under eyes
5. Part of atopic triad: atopic dermatitis, asthma, and allergic rhinitis
6. Decreased innate immunity in skin leads to increased susceptibility to bacterial and viral skin infections

45. Describe the five key battle plans to treat atopic dermatitis

1. **Reduce pruritus.** Topical corticosteroids and bland emollients help reduce pruritus. Oral antihistamines may also be used for their sedative effect at night and may reduce pruritus.
2. **Improve skin barrier.** Emollients (petrolatum and fragrance-free ointments and creams) prevent the evaporation of moisture via occlusion and are best applied immediately after bathing, when the skin is maximally hydrated, to "lock in" moisture. A "soak and smear" protocol is advisable in refractory cases.
3. **Reduce inflammation.** Topical steroids are invaluable as anti-inflammatory agents and can hasten the clearing of eruptions that are erythematous (inflamed). Medium-strength corticosteroids can be used on areas other than the face and occluded regions (diaper area); low-strength steroids (e.g., 1% hydrocortisone) may be used in these thin-skinned areas for limited periods. Topical calcineurin and phosphodiesterase

inhibitors are immunomodulators approved for the treatment of moderate to severe atopic dermatitis (see question 47).

4. **Control infection.** Superinfection with *S. aureus* is extremely common. First-generation cephalosporins such as cephalexin are the usual antibiotics of choice for infected atopic dermatitis. Dilute bleach baths or compresses are sometimes recommended two to three times per week to reduce staphylococcal colonization.
5. **Avoid irritants.** Gentle fragrance-free soaps and shampoos should be used; wool and tight synthetic garments should be avoided; tight nonsynthetic garments may help minimize the “itchy” feeling; consider furniture, carpeting, pets, and dust mites as possible irritants and/or trigger factors.

Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014;70(2):338–351.
Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71(1):116–132.
Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* 2014;71(2):327–349.

46. What is another use for dilute bleach in addition to getting stains out of clothing?

Dilute bleach baths or rinses have been used to treat superinfections and to prevent local skin infections in patients with atopic dermatitis. Mechanisms of action may include restoration of the surface microbiome by eradication of bacteria, particularly *S. aureus*, as well as anti-inflammatory and antipruritogenic effects. Caution must be exercised so that the bleach (sodium hypochlorite) is diluted before use and does not come into contact with eyes or mucous membranes.

Maarouf M, Shi V. Bleach for atopic dermatitis. *Dermatitis.* 2018;29(3):120–126.
Eriksson S, van der Plas MJA, Mörgelin M, et al. Antibacterial and antibiofilm effects of sodium hypochlorite against *Staphylococcus aureus* isolates derived from patients with atopic dermatitis. *Br J Dermatol.* 2017;177(2):513–521.

47. What topical options are available for children with atopic dermatitis who require continued and frequent use of topical steroids or whose parents are “steroid phobic”?

Calcineurin and **phosphodiesterase 4 (PDE4) inhibitors**. Both are anti-inflammatory agents approved for children $>$2 years of age with mild to moderate atopic dermatitis that have been shown to achieve lesion clearance, reduce relapse, and lower the need for topical steroids. Topical calcineurin inhibitors, pimecrolimus and tacrolimus, disrupt activation of T cells and mast cells and decrease cytokine production. A PDE4 inhibitor, crisaborole, also suppresses cytokine production. The most common side effect is stinging or burning sensation, especially during initial use. However, long-term side effects have not been fully evaluated.

Papier A, Strowd LC. Atopic dermatitis: a review of topical nonsteroid therapy. *Drugs Context.* 2018;7:212521.
Ahluwalia J, Udkoff J, Waldman A, et al. Phosphodiesterase 4 inhibitor therapies for atopic dermatitis: progress and outlook. *Drugs.* 2017;77(13):1389–1397.

48. Why is there a black box warning on topical calcineurin inhibitors?

The long-term side effects of chronic use are still under investigation. One prospective 5-year study found no impairment of humoral or cellular immunity. A black box warning is in place based on concerns regarding systemic absorption and the associated increased cancer risk in patient populations in which long-term systemic administration has occurred, such as organ transplant recipients. Patients should be instructed about the importance of sun protection while using topical immunosuppressive medications such as topical calcineurin inhibitors.

Sigurgeirsson B, Bozanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics.* 2015;135(4):597–606.
Thaçi D, Salgo R. Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. *Clin Dermatol.* 2010;28(1):52–56.

49. What targeted systemic therapy is available for atopic dermatitis?

Dupilumab is the first targeted systemic treatment approved for moderate to severe atopic dermatitis. It is a monoclonal antibody that acts as a receptor antagonist by binding to a subunit of the interleukin-4 receptor with modulation of the effects of cytokines interleukin-4 and interleukin-13. In 2019, dupilumab was approved by the FDA for patients ages 12 years and older with severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Treister AD, Lio PA. Long-term off-label dupilumab in pediatric atopic dermatitis: a case series. *Pediatr Dermatol.* 2019;36(1):85–88.
Gooderham MJ, Hong HC, Eshtiaghi P, Kapp KA. Dupilumab: a review of its use in atopic dermatitis. *J Am Acad Dermatol.* 2018;78(3 Suppl):S28–S36.

50. Why should fluorinated (halogenated) and other potent topical steroids not be used on the face?

- Facial skin is thinner, and therefore percutaneous absorption is higher.
- Telangiectasias, or spider veins, can occur.
- Cutaneous atrophy can occur.
- Perioral dermatitis or post-steroid rosacea can occur with rebound symptoms that are worse than the original rash.

51. Is there a genetic basis for atopic dermatitis?

It is likely that both genetic and environmental factors play a role. Susceptibility to atopic dermatitis is found in patients with genetic mutations in *filaggrin* (short for filament-aggregating protein), an epithelial protein that cross-links keratin and serves to waterproof the epidermis, or outer layer of skin. About 10% of individuals of European ancestry are at least heterozygous carriers for the gene, which results in a 50% decrease in the expressed filaggrin protein. This group is more likely to develop eczema of increased severity. Many children with atopic dermatitis have a family history of atopy; if one parent has atopy, 60% of offspring will be atopic; if two parents do, 80% of children are affected.

Cabanillas B, Novak N. Atopic dermatitis and filaggrin. *Curr Opin Immunol.* 2016;42:1–8.

Irvine AD, McLean WHI, Leung DYM. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med.* 2011; 365(14):1315–1327.

52. Why are patients with atopic dermatitis more susceptible to skin infections?

In addition to a diminished barrier function of skin layers, innate immunity in the skin is altered with lower levels and decreased functioning of antimicrobial peptides produced by keratinocytes. This leads to a lack of restriction of the growth of microorganisms and an increased susceptibility to infection with *S. aureus*.

Nowicka D, Grywalska E. The role of immune defects and colonization of *Staphylococcus aureus* in the pathogenesis of atopic dermatitis. *Anal Cell Pathol (Amst).* 2018;1956403.

53. What other skin conditions mimic atopic dermatitis?

- Seborrheic dermatitis
- Scabies
- Psoriasis
- Tinea capitis
- Lichen simplex chronicus
- Acrodermatitis enteropathica
- Contact dermatitis
- Langerhans cell histiocytosis
- Xerotic eczema (dry skin)
- Immunodeficiency disorders (e.g., Wiskott-Aldrich syndrome, hyperimmunoglobulin E syndrome, severe combined immunodeficiency)
- Nummular eczema
- Metabolic disorders (e.g., phenylketonuria, essential fatty acid deficiency, biotinidase deficiency)

54. What is the "atopic march"?

Approximately half of infants with atopic dermatitis will develop asthma, and two-thirds will develop allergic rhinitis. Thus the one condition in infancy "marches" toward others. Currently under study are ways to interrupt this progression.

Hill DA, Spergel JM. The atopic march: critical evidence and clinical relevance. *Ann Allergy Asthma Immunol.* 2018; 120(2):131–137.

55. What features help differentiate seborrheic dermatitis from atopic dermatitis during infancy?

See Table 4.1.

Table 4.1 Seborrheic Dermatitis Versus Atopic Dermatitis

CHARACTERISTICS	SEBORRHEIC DERMATITIS	ATOPIC DERMATITIS
Color	Salmon	Pink or red (if inflamed)
Scale	Yellowish, greasy	White, not greasy
Age	Infants <6 months or adolescents	May begin at 2-12 months and continue through childhood
Itching	Not present	May be severe
Distribution	Face, postauricular scalp, axillae, and groin	Cheeks, trunk, and extensors of extremities
Associated features	None	Dennie-Morgan folds, allergic shiners, hyperlinear palms
Lichenification	None	May be prominent
Response to topical steroids	Rapid	Slower

56. How should parents cope with cradle cap?

Seborrheic dermatitis of the scalp, also known as "cradle cap," occurs during infancy and presents as a yellow, greasy, scaling adherent rash on the scalp that may extend to the forehead, eyes, ears, eyebrows, nose, and back of the head. It appears during the first few months of life and generally resolves in several weeks to a few months. Treatment includes the application of mineral oil followed by shampooing with a mild antidandruff shampoo containing selenium sulfide. Parents should be cautioned to take extra care when washing the scalp because these shampoos may irritate the infant's eyes. A mild-potency topical steroid such as hydrocortisone (1% to 2.5%) may be needed for persistent areas. Families should be advised not to scrub or pick off the scale because the underlying skin is often tender and inflamed.

57. What condition causes bumps on the cheeks, upper arms, and thighs?

Associated both with atopic dermatitis and ichthyosis vulgaris, **keratosis pilaris** runs in families and is asymptomatic. It is characterized by spiny follicular papules, giving involved areas a "chicken skin" or "gooseflesh" feel (Fig. 4.10). Usual treatment is with bland emollients or emollients that contain a mild peeling agent, such as lactic acid, salicylic acid, or an alpha hydroxy acid preparation.

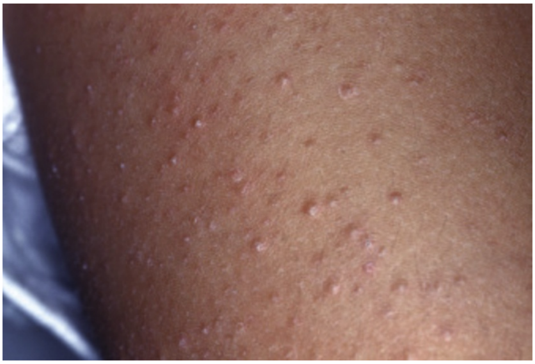

Fig. 4.10 Keratosis pilaris with keratotic follicular plugs and surrounding erythema. (From Kleigman RM, St Geme JW, Blum NJ, et al, eds. *Nelson Textbook of Pediatrics*. 21st ed. Philadelphia, PA: Elsevier; 2020:3505.)

58. What are the causes of irritant contact diaper rash?

A variety of local factors are involved. Diapers contribute to the chafing of the skin and the prevention of moisture evaporation, thus increasing epidermal hydration and permeability to irritants and mechanical injury. Proteolytic enzymes in urine and stool and ammonia generated from urine irritate chafed skin. Seasoned pediatricians will advise that alcohol-based diaper wipes may feed the flames of diaper rash.

Shin H. Diagnosis and management of diaper dermatitis. *Pediatr Clin North Am.* 2014;61(2):367–382.

59. What features of diaper rash suggest more sinister diseases?

- Marked tenderness, rapid onset (staphylococcal scaled skin syndrome)
- Deep ulcerations, vesicles (herpes simplex)
- Perianal erythema (perianal strep)
- Beefy red, erosive, extensive lesions (particularly intertriginous) that are poorly responsive to topical steroids and antifungals (Langerhans cell histiocytosis, acrodermatitis enteropathica, immunodeficiency states)
- Extensive and severe lesions with pungent odor (abuse or neglect with infrequent changing)

Shin H. Diagnosis and management of diaper dermatitis. 2014;*Pediatr Clin North Am.* 2014;61(2):367–382.

60. Are topical steroid/antifungal preparations useful for treating children with diaper dermatitis?

Most diaper dermatitis is usually diagnosed as either irritant contact dermatitis or candidal dermatitis. Irritant diaper dermatitis responds well to very-low-potency topical corticosteroids (as a result of their anti-inflammatory properties) and a topical barrier such as zinc oxide ointment. Candidiasis of the diaper area responds well to topical antifungal preparations; rarely, an oral anticandidal medication is necessary. Combination preparations containing both antifungal and corticosteroid medications are not recommended to treat diaper dermatitis because the strength of the steroid component in these products is usually too high for use in the diaper area.

Kazaks EL, Lane AT. Diaper dermatitis. *Pediatr Clin North Am.* 2000;47(4):909–920.

61. Which dietary deficiencies may be associated with an eczematous dermatitis?

Deficiencies in **zinc**, **biotin**, **essential fatty acids**, and **protein** (kwashiorkor) may be associated with eczematous dermatitis.

62. What are the two main types of contact dermatitis?

Irritant and **allergic**. Irritant contact dermatitis arises when agents such as harsh soaps, bleaches, or acids have direct toxic effects when they contact the skin. Allergic contact dermatitis is a T-cell–mediated inflammatory immune reaction that requires sensitization to a specific antigen.

Kostner L, Anzengruber F, Guillod C, et al. Allergic contact dermatitis. *Immunol Allergy Clin North Am.* 2017;37(1):141–152.

63. What type of agents can cause allergic contact dermatitis in children?

Allergic contact dermatitis can occur in all age groups, but it is often underrecognized in pediatric patients. Sensitizers include plant resins (poison ivy, sumac, or oak); nickel in jewelry, metal snaps, and belts; fragrance; topical antibiotics, including bacitracin and neomycin; wool wax alcohols and lanolin in moisturizers; preservatives; fabric dyes; and materials used in shoes, including adhesives, rubber accelerators, and leather tanning agents. Of note, allergic contact dermatitis due to metals in mobile phones and other portable electronic devices, especially nickel and chromium, has been on the rise in recent years.

Jacob SE, Admani S. iPad—increasing nickel exposure in children. *Pediatrics.* 2014;134(2):e580–e582.

Zug KA, Pham AK, Belsito DV, et al. Patch testing in children from 2005 to 2012: results from the North American contact dermatitis group. *Dermatitis.* 2014;25(6):345–355.

64. When does the rash in poison ivy appear relative to exposure?

Poison ivy, or rhus dermatitis, is a typical delayed hypersensitivity reaction. The time between exposure and cutaneous lesions is usually 2 to 4 days. However, the eruption may appear as late as a week or more after contact in individuals who have not been previously sensitized. The oil resin must be washed off of fomites (i.e., objects or materials such as shoes, shoelaces, or sports equipment) to try to prevent a prolonged reaction.

65. What is the "id" reaction?

Your superego will be stroked if you identify the "id" reaction in a confusing dermatologic case. This reaction is the generalization of a local inflammatory dermatitis (e.g., contact dermatitis, tinea capitis after treatment) to sites that have not been directly involved with the offending agent. The exact mechanism remains unclear, but it may be immune complex mediated.

66. How does the vehicle used in a dermatologic preparation affect therapy?

In general, acute lesions (moist, oozing) are best treated with aqueous, drying preparations (solution or gel). Chronic, dry lesions fare better when a lubricating, moisturizing vehicle is used (cream or ointment). As a rule, any vehicle that enhances hydration of the skin enhances the percutaneous absorption of topical medications (most of which are water soluble). Thus in preparations of equal concentration, the potency relationship is ointment $>$ cream $>$ gel $>$ lotion. See Table 4.2.

Table 4.2 Vehicles Used in Dermatologic Preparations

Drying Vehicles	
Lotion:	A suspension of powder in water; therapeutic powder remains after aqueous phase evaporates; useful in hairy areas, particularly the scalp
Solution:	Transparent alcohol containing vehicle; evaporates leaving skin drier; may be irritating for sensitive inflamed skin; useful in oily skin, hairy areas, particularly the scalp
Gel:	Transparent emulsion that liquifies when applied to skin; most useful for acne preparations and tar preparations for psoriasis
Pastes:	Combination of powder (usually cornstarch) and ointment; stiffer than ointment
Moisturizing Vehicles	
Creams:	Mixture of oil in a water emulsion; more useful than ointments when environmental humidity is high and in naturally occluded areas; less greasy than ointment
Ointments:	Mixture of water in an oil emulsion; also has an inert petroleum base; longer lubricating effect than cream

FUNGAL INFECTIONS

67. What are the most common causes of tinea capitis?

Tinea capitis is a dermatophytic infection of the scalp, eyebrows, and eyelashes. Dermatophytes are fungi that require keratin for growth. In the United States, the most common cause is ***Trichophyton tonsurans***. Worldwide, the most common cause is ***Microsporum canis***.

68. What are the main clinical features of tinea capitis?

Tinea capitis presents with a variety of morphologic characteristics, including scalp scaling, alopecia, erythema, papules, pustules, "black dot" tinea, or a kerion (a boggy, tender mass). The "black dot" presentation occurs when the infected hair shaft breaks at the surface of the scalp, leaving a bald patch with black dots (or lighter dots, depending on hair color) (Fig. 4.11). Regional adenopathy is very common with inflammatory tinea.

Hubbard TW. Predictive value of symptoms in diagnosing childhood tinea capitis. *Arch Pediatr Adolesc Med.* 1999; 153(11):1150–1153.

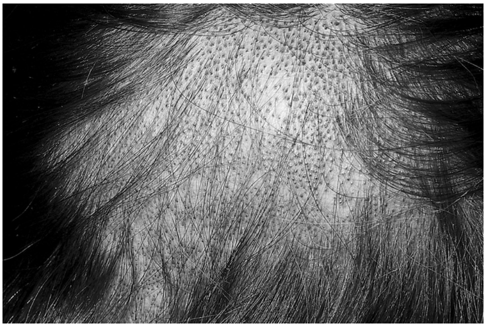

Fig. 4.11 Black dot tinea. (From Schachner LA, Hansen RC, eds. *Pediatric Dermatology*. 3rd ed. Edinburgh, Scotland: Mosby; 2003:1096.)

69. What is a kerion?

A *kerion* is a fluctuant and tender mass that occurs in some cases of tinea capitis. It can be associated with alopecia, pustules, and purulent drainage. It is believed to be primarily an excessive inflammatory response to tinea, and thus, initial treatment consists of systemic antifungal agents, principally griseofulvin (>2 years) or terbinafine (>4 years), and selenium sulfide shampoo. Prompt diagnosis and management are important to minimize the potential for permanent scarring. Short courses of oral steroids can be considered in those lesions that are exquisitely painful. Secondary bacterial infection should be ruled out with culture.

Honig PJ, Caputo GL, Leyden JJ, et al. Microbiology of kerions. *J Pediatr.* 1993;123(3):422–424.

70. Why is it necessary to culture for tinea capitis?

Tinea capitis can be caused by a variety of dermatophyte fungal organisms, and over the last decade, resistance to commonly used treatments (griseofulvin) has been noted. Children with tinea capitis are requiring longer courses of treatment and higher doses of medication to eradicate the fungal infection. Moreover, other conditions (e.g., alopecia areata, psoriasis of the scalp) may be confused with tinea capitis. Therefore, just like for other pediatric infections, it is important to document the type of infection with a culture so that proper treatment may be administered. Newer, more rapid diagnostic methods, including molecular techniques such as polymerase chain reaction (PCR), multiplex ligation-dependent probe amplification (MLPA), and rolling circle amplification (RCA), are currently under study.

Hay RJ. Tinea capitis: current status. *Mycopathologia.* 2017;182(1):87–93.

71. How can a culture be obtained if fungal culture medium is not available in the office?

The simplest method is to take a cotton swab culturette and moisten it with sterile water. Then, take the swab and rub it over the affected areas and all four quadrants of the scalp. The cotton swab can be used to directly inoculate the fungal culture media if you have it in the office or may be transported back to the laboratory for inoculation.

Friedlander SF, Pickering B, Cunningham BB, et al. Use of the cotton swab method in diagnosing tinea capitis. *Pediatrics.* 1999; 104(2 Pt 1):276–279.

KEY POINTS: MAIN FEATURES OF TINEA CAPITIS

1. Scaly alopecia
2. Black-dot hairs often observed
3. Associated with posterior cervical adenopathy
4. Potassium hydroxide test often positive
5. Diagnosis confirmed by positive fungal culture
6. Most common cause in United States: *T. tonsurans*

72. How should children with tinea capitis be treated?

The dermatophytes that cause tinea thrive deep in the hair shaft, beyond the reach of topical therapy alone. Recommended therapy includes systemic courses of griseofulvin or terbinafine. The choice of medication should be individualized based on culture results (griseofulvin remains the treatment of choice for *Microsporum* species), cost, duration of therapy, and consideration of compliance. Oral griseofulvin (microsize or ultramicrosize preparation) has a long-term safety profile in children. It is given with fatty foods such as milk or ice cream to facilitate absorption. Terbinafine is FDA-approved for the treatment of tinea capitis in children $\geq$4 years.

Gupta AK, Mays RR, Versteeg SG, et al. Tinea capitis in children: a systematic review of management. *J Eur Acad Dermatol Venereol.* 2018;32(12):2264–2274.

Moriarty B, Hay R, Morris-Jones R. The diagnosis and management of tinea. *BMJ.* 2012;345:e4380.

73. Can topical therapy be used for the treatment of onychomycosis (tinea unguium) in children?

Onychomycosis is a chronic, recurrent infection of the nail caused by dermatophytes, yeasts, and non-dermatophytic molds. The majority of cases are caused by dermatophytes, particularly *Trichophyton rubrum.* Systemic antifungal medications are thought to be more effective than topical antifungals. However, given the potential risk for and need to monitor for liver toxicity, topical medication represents an attractive option for treatment. A drawback to topical use is the requirement for prolonged durations of therapy. Additionally, clinical data regarding topical treatment efficacy are limited. Newer topical agents (efinaconazole and tavaborole) are under study. Prevention of recurrence is an important component of treatment. The biggest risk factor for onychomycosis in children is a family member or close contact with onychomycosis or tinea pedis. Counseling on ways to reduce transmission and spread should go hand in hand (or nail in nail) with treatment.

Gupta AK, Mays RR, Versteeg SG, et al. Onychomycosis in children: safety and efficacy of antifungal agents. *Pediatr Dermatol.* 2018;35(5):552–559.

Eichenfield LF, Friedlander SF. Pediatric onychomycosis: the emerging role of topical therapy. *J Drugs Dermatol.* 2017; 16(2):105–109.

74. How can one reduce the spread of tinea infections?

Tinea infections are transmitted person to person or animal to person by direct or indirect contact, including the back of seats, hair brushes or hair clips, caps, towels, or clothing contaminated with hair. Therefore reducing exposure to these modes of transmission can help reduce the spread of infection. Additionally, washing the hair with a selenium sulfide shampoo more frequently may help reduce scale and therefore reduce the quantity of infectious particles that are easily dislodged from the hair and scalp.

American Academy of Pediatrics. Infections spread by direct contact. In Kimberlin DW, Brady MT, Mary Jackson MA, Long SS, eds. *Red Book: 2018 Committee on Infectious Diseases*. 31st ed. Itasca, IL; American Academy of Pediatrics; 2018:141–142.

75. How should children who are receiving systemic medication for tinea infections be monitored?

The incidence of hepatitis or bone marrow suppression from *griseofulvin* in children is rare. Children who are undergoing an acute course of treatment (6 to 8 weeks) do not need obligatory blood counts or liver function tests. However, a history of hepatitis or associated symptoms would warrant a pretreatment evaluation of liver function and intermittent monitoring. Resistance to griseofulvin is increasing, and higher, longer dosing may be needed to achieve clinical cure. For those rare cases in which griseofulvin is going to be used for >2 months, one should consider obtaining complete blood counts and liver function tests on an every-other-month basis. When using *terbinafine,* a complete blood count and hepatic function panel are recommended at baseline, and patients should be warned/monitored for evidence of side effects such as hepatotoxicity. Some experts recommend repeat testing 4 to 6 weeks into therapy. Rare cases of hepatic failure and bone marrow suppression have been reported.

Patel D, Castelo-Soccio LA, Rubin AI, Streicher JL. Monitoring during systemic terbinafine therapy for pediatric onychomycosis. *JAMA Dermatol.* 2017;153(12):1326–1327.

76. What puts the "versicolor" in tinea versicolor?

A very common superficial disorder of the skin, tinea versicolor (also known as *pityriasis versicolor*) is caused by the yeast form of *Malassezia furfur*, known as *Pityrosporum orbiculare* and *Pityrosporum ovale*. It appears as multiple macules and patches with fine scales over the upper trunk; arms; and, occasionally, the face and other areas (Fig. 4.12). Lesions are "versatile" in color (i.e., light tan, reddish, or white) and may be "versatile" by season (i.e., lighter in summer and darker in winter compared with surrounding skin). The yeast interferes with melanin production, possibly by the disruption of tyrosinase activity, at the involved sites. Diagnosis can be confirmed with a KOH preparation of a scraping from the involved skin, which has characteristic fungal hyphae and a grapelike spore pattern referred to as a "spaghetti and meatball" appearance. Dyspigmentation may persist for months after treatment.

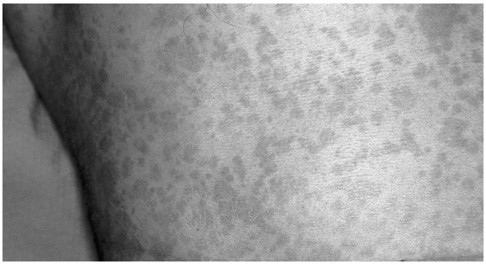

Fig. 4.12 Tinea versicolor on the chest. (From Gawkrodger DJ. *Dermatology: An Illustrated Colour Text*. 3rd ed. London: Churchill Livingstone; 2002:38.)

77. How is tinea versicolor treated?

- **Selenium sulfide 2.5% lotion:** The shampoo or lotion is applied over the affected area nightly and left on overnight during the first week, with decreasing frequency over the ensuing weeks. Monthly application may decrease recurrences.
- **Ketoconazole 2% shampoo:** The shampoo is applied to wet skin and lathered. Patients are instructed to let the shampoo remain in place without washing for 3 to 5 minutes. Treatment is repeated for 1 to 3 days in a row. Monthly prophylactic treatments are suggested to prevent recurrence.
- **Topical antifungal creams:** May be applied once to twice daily to limited areas. This is generally less favored in diffuse disease, which is commonly seen.
- **Oral antifungal agents:** These treatments, which are sometimes effective after a single one-time dose, may be considered off-label in severe diffuse or recalcitrant tinea versicolor in older children and adolescents. However, side effects, including liver toxicity, should be considered.

78. Which rashes resemble tinea pedis (athlete's foot) in children?

- **Dyshidrotic eczema**: Erythema with microvesicles of interdigital spaces and lateral feet
- **Contact dermatitis**: Typically involves dorsum of feet and spares interdigital spaces
- **Juvenile plantar dermatosis**: Glazed erythema and fissuring of toes and distal soles; often pruritic
- **Pitted keratolysis**: Small pits that may converge to superficial erosions on the sole of the foot; hyperhidrosis and malodor are common; associated with *Corynebacterium* species or *Micrococcus sedentarius* infections

79. How does one differentiate between irritant diaper dermatitis and candidal diaper dermatitis?

Both types of dermatitis often present together. Classic irritant diaper dermatitis involves the skin, which contacts the diaper with sparing of the protected skin folds. Candidal dermatitis, on the other hand, favors skin folds such as the inguinal folds and intragluteal cleft. In clinical practice, candidal infection is a common infection that can be precipitated by the compromise of the cutaneous barrier seen in irritant dermatitis. With candida infection, one typically sees confluent, beefy red plaques involving the groin creases. Scale and satellite papules or pustules are commonly seen at the periphery of the plaque. The diagnosis can be made clinically and with a KOH preparation and yeast culture. Treatment comprises a topical anticandidal agent such as clotrimazole and use of a thick barrier cream, such as zinc oxide. A few days of a low-potency corticosteroid ointment may reduce the erythema significantly. Remember to consider other causes, such as seborrheic dermatitis, psoriasis, acrodermatitis enteropathica, Langerhans cell histiocytosis, or immunodeficiency, for chronic and refractory diaper dermatitis.

HAIR AND NAIL ABNORMALITIES

80. How fast does hair grow?

Hair grows about **1 cm per month**.

81. What causes sparse or absent hair in children?

- *Congenital localized*: nevus sebaceous (or sebaceous), aplasia cutis, incontinentia pigmenti, focal dermal hypoplasia, intrauterine trauma, infection (e.g., herpes)
- *Congenital diffuse*: loose anagen syndrome, Menkes syndrome, trichoschisis (broken or split hairs), genetic syndromes (e.g., ectodermal dysplasia, lamellar ichthyosis, Netherton syndrome)
- *Acquired localized*: tinea capitis, alopecia areata, traction alopecia, traumatic scarring (e.g., trichotillomania), androgenic alopecia, Langerhans cell histiocytosis, lupus erythematosus
- *Acquired diffuse*: telogen effluvium, anagen effluvium, acrodermatitis enteropathica, endocrinopathies (e.g., hypothyroidism)

Datloff J, Esterly NB. A system for sorting out pediatric alopecia. *Contemp Pediatr.* 1986;3:53–56.

82. Which kind of alopecia simply requires a change in hairstyle as the treatment?

Traction alopecia. This condition is due to styling with tight braids or ponytails that create tension on the hair shaft. This process damages the area, which serves as the source of new cells for the hair follicle. An erythematous, papular, or papulopustular reaction may be seen. Treatment involves loose hair styles, avoiding chemical processing or heat treatments. With appropriate changes in hairstyling early on, the prognosis is excellent. However, if the process continues, it may result in scarring alopecia.

Castrelo-Soccio, L. Diagnosis and management of alopecia in children. *Pediatr Clin North Am.* 2014;61(2):427–442.

83. How can alopecia areata be differentiated clinically from tinea capitis?

In *tinea capitis,* the fungal organism invades the hair shaft, but is also present in the epidermis (the top layer of the skin). There are usually changes of scaling and inflammatory lesions that are intermingled with black dots representing broken hairs. In *alopecia areata,* the scalp is smooth, although patches may be pink to peach colored (Fig. 4.13). Some hairs within the patch may have a tapered appearance, with the wider end distally and a thinner end at the base of the scalp (i.e., the "exclamation point hair"). There is no lymphadenopathy in patients with alopecia areata, but this is not uncommon in patients with tinea capitis. The gold standard for diagnosis of tinea is a positive fungal culture.

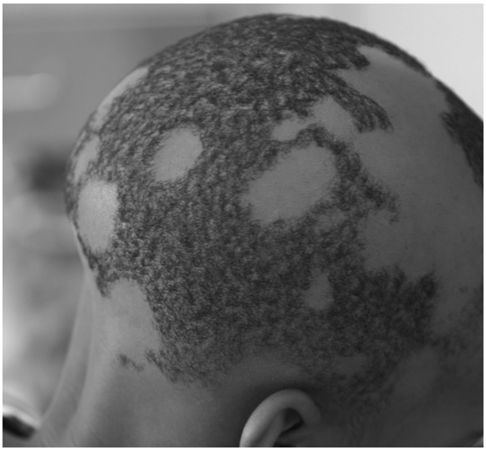

Fig. 4.13 Well-demarcated, hairless patches of alopecia areata.

84. What are reported as poor prognostic indicators for recovery of hair in patients with alopecia areata?

- Atopy
- Presence of other immune-mediated disease (e.g., thyroid disease, vitiligo)
- Family history of alopecia areata (about 25% of patients)
- Young age at onset
- Longer duration of active disease

Gilhar A, Etzioni A, Paus R. Alopecia areata. *N Engl J Med.* 2012;366(16):1515–1525.
Uchiyama M, Egusa C, Hobo A, et al. Multivariate analysis of prognostic factors in patients with rapidly progressive alopecia areata. *J Am Acad Dermatol.* 2012;67(6):1163–1173.

85. What are treatments for alopecia areata?

Treatment is based on the extent of disease: patchy, totalis (loss of all scalp hair), or universalis (loss of all body hair). Although the cause is unknown, alopecia areata is generally considered to be a T-cell–mediated autoimmune disorder. Therefore treatments are directed at suppressing the immune response around the hair follicle. Topical or intralesional corticosteroids are the mainstays of therapy. Systemic corticosteroids are rarely used chronically because of side effects. Anthralin, as an irritant, or other topical sensitizers are designed to cause a mild dermatitis and theoretically alter local immunity to promote hair regrowth. Other systemic immunosuppressive treatments, including methotrexate and cyclosporine, have been tried in adult patients with alopecia areata; however, because of the potential for side effects, they are not typically employed in children. Studies in children are ongoing regarding the utility of Janus kinase (JAK) inhibitors, which interfere with the JAK-STAT (Janus Kinase-Signal Transducer and Activator of Transcription) signaling pathway and suppress cell-mediated inflammatory conditions. JAK inhibitors have shown efficacy in a variety of autoinflammatory conditions. The option of not treating must be reviewed with the family. Support groups should be offered, and many patients have had improved self-esteem after being fitted with a hair prosthesis.

Iorizzo M, Tosti A. Emerging drugs for alopecia areata: JAK inhibitors. *Expert Opin Emerg Drugs.* 2018;23(1):77–81.
Castrelo-Soccio, L. Diagnosis and management of alopecia in children. *Pediatr Clin North Am.* 2014;61(2):427–442.
Children's Alopecia Project. www.childrensalopeciaproject.org. Accessed January 18, 2020.
National Alopecia Areata Foundation. www.naaf.org. Accessed January 18, 2020.

86. You are evaluating a healthy 4-year-old with fine, sparse hair who has never had a haircut. What condition do you suspect?

Loose anagen syndrome is typically seen in 2- to 5-year-old blond girls, but may also present in children with darker hair. The hair is of variable lengths and is easily pulled from the scalp. A microscopic examination of a few pulled hairs reveals predominance of anagen hair bulbs with ruffled cuticles. There are no associated nail, skin, or teeth findings in loose anagen syndrome. There is no treatment, but gentle hair styling should be encouraged. Fortunately, the condition tends to improve over time.

Alves R, Grimalt R. Hair loss in children. *Curr Probl Dermatol.* 2015;47:55–66.
Dhurat RP, Deshpande DJ. Loose anagen hair syndrome. *Int J Trichology.* 2010;2(2):96–100.

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87. What is the likely diagnosis in a child who develops diffuse hair loss 3 months after major surgery?

Telogen effluvium. This is the most common cause of acquired diffuse hair loss in children. In a healthy individual, most hairs are present in a growing (anagen) phase. After a physical or emotional stress, such as a significant fever, illness, pregnancy, birth, surgery, or large weight loss, a large number of scalp hairs can convert to the resting (telogen) phase. About 2 to 5 months after the stressful event, the hair begins to shed, at times coming out in large clumps. The condition is temporary and usually does not produce a loss of more than 50% of the hair. When the hair roots are examined, there is a characteristic lighter-colored root bulb, which characterizes a telogen hair. The hair loss can continue for 6 to 8 weeks, at which time new, short, regrowing hairs should be visible. The differential diagnosis for telogen effluvium includes nutritional deficiencies and abnormal thyroid function.

Anagen effluvium, the loss of growing hairs, is most commonly seen during radiation and chemotherapy treatments for cancer.

88. What is the likely reason for noticeable occipital hair loss in a healthy 3-month-old infant?

Hair loss in infants, in particular on the occipital scalp, is usually a normal finding and a variant of telogen effluvium. Telogen shedding occurs in the occipital scalp typically at 2 to 3 months of life. Pressure and rubbing from sleeping on the back may accentuate this hair loss. Reassurance and monitoring should be provided to the parent. Of note, the first *in utero* anagen phase starts at about 18 to 20 weeks of gestation. While the occipital scalp normally sheds after birth at approximately 2 to 3 months of age, the remaining scalp is expected to have telogen shedding a bit later, between 4 and 8 months. This normal and predictable hair loss progression has sometimes been called (with a smile) “baby-patterned baldness.”

89. Are most hairs growing or resting?

Most infants and children have about 90% of scalp hair in the **growing** (anagen) state and about 10% in the resting (telogen) state. On average, a single scalp hair will grow for about 3 years, rest for 3 months, and then, upon falling out, be replaced by a new growing hair.

90. What puzzling cause of asymmetric hair loss in a child will sometimes cause an intern to pull his or her hair out?

Trichotillomania is hair loss as a result of self-manipulation, such as rubbing, twirling, or pulling. Hair loss is asymmetric. The most common physical finding is unequal hair lengths in the same region without evidence of epidermal changes of the scalp. Evidence of both alopecia areata and trichotillomania may occur in the same patient. Parents often do not observe the causative behavior, and convincing them of the likely diagnosis may take some effort. Behavior modification is often the first line of treatment. In younger children, the hair-pulling behavior usually resolves; in older children, it may persist and require psychiatric referral for additional management. Rarely, a child will swallow the hair and develop vomiting because of the formation of a gastric trichobezoar (hairball).

91. What causes green hair?

Children with blond or light-colored hair can develop green hair after long-term exposure to **chlorinated swimming pools**. It is the result of the incorporation of copper ions into the hair matrix. OTC chelating shampoos are available for prevention and treatment.

92. How should ingrown toenails be managed?

Soaks, open-toed sandals, properly fitting shoes, topical or systemic antibiotics, incision and drainage, or surgical removal of the lateral portion of the nail may all be used. Control is best obtained by letting the nail grow beyond the free end of the toe. Proper instruction on nail care, including straight rather than arc trimming, is mandatory.

93. Which pathogens are responsible for paronychia?

- *Acute paronychia* (inflammation of the nail fold, usually with abscess formation) is most commonly caused by *S. aureus*. The proximal or lateral nail fold becomes intensely erythematous and tender. If a collection of pus develops at this site, it should be incised and drained. The treatment of acute paronychia includes the oral administration of antistaphylococcal antibiotics.
- *Chronic paronychia* is most often caused by *Candida albicans* and often involves a history of chronic water exposure (e.g., dishwashing, thumb sucking). Although rarely inflamed, there is edema of the nail folds and separation of the folds from the nail plate. The nails may become ridged and develop a yellow-green discoloration. A bacterial culture may reveal a variety of gram-positive and gram-negative organisms. Therapy includes topical antifungal agents and avoidance of water. There is no place for griseofulvin in the treatment of chronic paronychia.

94. A healthy 7-year-old child who develops progressive yellowing and increasing friability of all nails over a period of 12 months likely has what condition?

Twenty-nail dystrophy (trachyonychia). The progressive development of rough nails with longitudinal grooves, pitting, chipping, ridges, and discoloration occurring in isolation in school-age children has been given this name, although not all nails need be involved. The etiology remains unclear, and a majority of cases resolve spontaneously without scarring. The nail changes, however, may be associated with other conditions, such as alopecia areata, lichen planus, psoriasis, and atopic dermatitis.

95. What nail change may follow hand–foot–mouth disease (HFMD) several weeks after the other hand and foot changes have resolved?

Onychomadesis is separation of the proximal nail plate from the nail bed, which is believed to be caused by arrest of nail growth. It is most commonly associated with illness and appears several weeks afterwards. There are now numerous reports of onychomadesis after HFMD caused by Coxsackie virus, but this may occur after other viral illnesses as well.

Chu DH, Rubin AI. Diagnosis and management of nail disorders in children. *Pediatr Clin North Am.* 2014;61(12):293–308.

96. What nail change is self-induced by the patient?

Habit tic deformity, which is caused by habitual picking of the proximal nail fold leading to inflammation and compression of the nail matrix. The characteristic nail changes are numerous transverse grooves. It is a type of onychotillomania.

Lipner SR. Habit tic nail deformity. *J Cutan Med Surg.* 2018;22(2):222.

97. What neurocutaneous condition may present with bumps around the nails?

Periungual fibromas are growths around the nails, which may begin to appear in patients with tuberous sclerosis around puberty. Incontinentia pigmenti may also present with nail findings, most often dystrophy, but subungual or periungual tumors may also occur.

98. What nail fold changes may be a sign of autoimmune collagen vascular disease?

Nail fold capillaries. These may be visualized in the proximal nail folds (the skin overlapping the base of the nails) in patients with collagen vascular diseases, such as systemic lupus erythematosus, dermatomyositis, and scleroderma. Nail fold capillaries are believed to reflect the microvascular abnormalities present in these rheumatologic conditions.

99. Are white spots on the nails a cause for concern?

It depends on the pattern. Small white spots on the nails, *leukonychia punctata,* are common and not often a cause for concern. They are most often the result of trauma to the nail bed, which "grow out" and resolve over time. On the other hand (or nail), transverse horizontal white lines, *leukonychia striata* or Mees lines, along the nail plate can be a manifestation of arsenic or thallium toxicity. Other toxins and drugs that are less commonly reported to induce Mees lines include carbon monoxide, chemotherapeutics, other heavy metals (e.g., lead, strontium), pilocarpine, and sulfonamides. Mees lines are also seen in systemic illnesses, such as renal disease, cardiac failure, and malignancy.

Zaniac MN, Walker A. Nail abnormalities associated with systemic pathologies. *Clin Dermatol.* 2013;31(5):627–649.

100. What is the significance of the great toenails deviating to the side?

Congenital malalignment of the great toenail is characterized by lateral deviation of nail plates frequently associated with nail dystrophy. The appearance of nail dystrophic changes (e.g., discoloration, nail plate thickening, transverse grooves) may be delayed with onset during childhood or puberty. It is probably underdiagnosed and treated unnecessarily. Ingrown toenails and onychogryphosis (nail hypertrophy) are among the most common complications. The etiology and pathogenesis are unclear, but it may be an autosomal dominant disorder with variable expressivity. Both great toenails are usually involved, but unilateral involvement has been reported.

Catalfo P, Musumeci ML, Lacarrubba F, et al. Congenital malalignment of the great toenails: a review. *Skin Appendage Disord.* 2018;4(4):230–235.

INFESTATIONS

101. How do lice differ?

- **Pediculosis capitis** (head lice): *Pediculus capitis,* the smallest and most common of the three human lice, is an obligate human parasite. Spread occurs directly by contact with an infected individual or indirectly through the use of shared combs, brushes, or hats. Infestation is more common in fine versus coarse hair types.
- **Pediculosis corporis** (body lice): *Pediculus humanus,* the largest (2 to 4 mm) of the three types, is usually associated with poor hygiene. It does not live on the body, but instead in the seams of clothing. It can be a vector for other diseases, such as epidemic typhus, trench fever, and relapsing fever.

- **Pediculosis pubis** (pubic lice): *Phthirus pubis* is also known as the *crab louse* because it is a broad insect with legs that look like crab claws. It is sometimes mistaken for a brown freckle. Acquisition is primarily through sexual contact.

102. What are the clinical findings of head lice infestation?

Scalp pruritus is most common, but many children are **asymptomatic**. A search for lice should be made in any school-age child presenting with scalp itching. Nits (lice eggs) are found in greatest density on the parietal and occipital areas.

103. How is the diagnosis of head lice made?

On physical examination, an actual louse (wingless, grayish insect about 3 to 4 mm) may be difficult to find, although one should easily be able to find nits. The nits are first attached to the hair close to the surface of the scalp and are oval and flesh-colored (Fig. 4.14). They are not easily removed from the hair shaft (compared with hair casts, dandruff, and external debris). Overdiagnosis of head lice is common. Microscopic evaluation of the suspected nit can confirm the diagnosis. When the louse emerges, the empty egg case, or nit, appears white in color and remains firmly attached to the hair shaft as the hair grows out (see Fig. 4.14).

Pollack RJ, Kiszewski AE, Spielman A. Overdiagnosis and consequent mismanagement of head louse infestations in North America. *Pediatr Infect Dis J.* 2000;19(8):689–693.

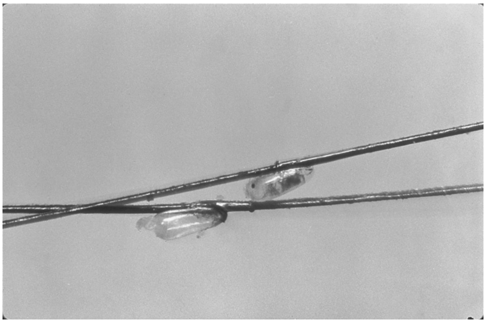

Fig. 4.14 Viable head louse egg *(right)* and hatched empty nit *(left)* attached to a child's hair. (From Schachner LA, Hansen RC, eds. *Pediatric Dermatology*. 3rd ed. Edinburgh, Scotland: Mosby; 2003:1143.)

104. What types of treatment are available for head lice?

- **Permethrin:** 1% and 5% (Nix, Elimite)
- **Pyrethrins:** (RID, A-200, R&C) (Resistance is increasing in these OTC products.)
- **Malathion:** 0.5% (Ovide is FDA-approved for the treatment of head lice in children 6 years and older; it is contraindicated in children under 2 years of age.)
- **5% Benzyl Alcohol Lotion:** (Ulesfia is FDA-approved for treatment of head lice in children 6 months of age and older.)
- **Asphyxiants:** Examples: petroleum jelly (Vaseline), mayonnaise, olive oil. (These have questionable efficacy and are messy!)
- **Ivermectin:** 0.5% lotion (Sklice is FDA-approved for treatment of head lice in children 6 months of age and older.)
- **Lindane:** 1% (Kwell is not recommended given the "black box warning" regarding serious neurotoxicity.)
- **Nit picking:** (see question 106.)

Devore CD, Schutze GE; Council on School Health and Committee on Infectious Diseases, American Academy of Pediatrics. Head lice. *Pediatrics.* 2015;135(5):e1355–e1365.

Pariser DM, Meinking TL, Bell M, et al. Topical 0.5% ivermectin lotion for treatment of head lice. *N Engl J Med.* 2012;367(18):1687–1693.

105. What precautions should be taken before prescribing malathion 0.5% lotion (Ovide) for head lice?

Malathion, a weak organophosphate cholinesterase inhibitor, is an approved prescription topical treatment for resistant head lice and their eggs. It is approved for use in children ≥6 years of age. It is contraindicated for neonates and infants. Because it is flammable, malathion should never be used near an open flame or heat source. It should be used in a well-ventilated area given its odor, and precautions also include increased absorption through open sores.

106. Should parents nit pick?

Once an infestation of lice has been properly treated, the nits are not viable or contagious. Despite this, many schools will not allow children with nits to attend, even though this nit-free policy has not been shown to be of benefit for controlling outbreaks. Increasing resistance to therapy may make removal more important to avoid diagnostic confusion. Manual removal (nit picking) is the most effective method; however, it is time consuming and tedious. Fine-toothed combs, such as the LiceMeister comb (available through the National Pediculosis Association at www.headlice.org) or other fine-toothed veterinary combs, aid in the removal.

107. How is a skin scraping for scabies, or “scabies prep,” done?

Because the highest percentage of mites are usually concentrated on the hands and feet, the web spaces between digits are the best places to look for the characteristic linear burrows. Moisten the skin with alcohol or mineral oil, scrape across the area of the burrow with a small, rounded scalpel blade (e.g., no. 15 or blunt-edged Fomon blade), and place the scrapings on a glass slide with a drop of KOH (or additional mineral oil, if used) and a cover slip. Burrows, if unseen, can be more precisely localized by rubbing a washable felt-tip marker across the web space and removing the ink with alcohol (called the *burrow ink test*). If burrows are present, ink will penetrate through the stratum corneum and outline the site. Under the microscope, mites, eggs, and/or scybala (mite feces) may be seen (Fig. 4.15).

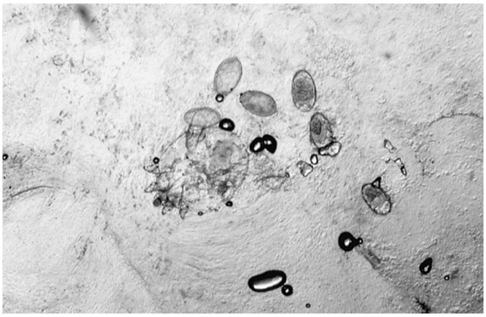

Fig. 4.15 Scabies mite and eggs. (From Gates RH, ed. *Infectious Disease Secrets*. 2nd ed. Philadelphia, PA: Hanley & Belfus; 2003:356.)

108. What treatment eliminates the scabies’ babies?

The treatment of choice for treating scabies is permethrin 5% cream (Elimite, Acticin). It may be used in children as young as 2 months old with a low risk for neurotoxicity. It is more effective and preferred over Lindane, which has a much higher potential risk for neurotoxicity.

Permethrin cream is applied from the neck to the toes at night with removal after 8 to 14 hours by bathing or showering. The scalp is also treated in infants and younger children without a full head of hair. Retreatment in 1 week is recommended. Physicians must make patients aware of the fact that lesions and pruritus may linger for at least 2 weeks after effective therapy. Antihistamines and low-potency topical steroids may help control symptoms. It must be stressed that all family members and close contacts should be treated simultaneously.

Gunning K, Kiraly B, Pippit K. Lice and scabies: treatment update. *Am Fam Physician.* 2019;99(10):635–642.

109. Which areas of the body are more commonly involved in scabies in younger children compared with adults?

- *Infants and children:* axillae with nodules and scalp, face, soles, and dorsal foot
- *Adults:* interdigital

Boralevi F, Diallo A, Miquel J, et al. Clinical phenotype of scabies by age. *Pediatrics.* 2014;133(4):e910–e916.

110. Why is it important to examine the nails in patients suspected of having scabies?

Scabies infestation may cause nail abnormalities, including paronychia, in a subset of patients. Nail thickening (hyperkeratosis), separation, or splitting of the nail tip (onycholysis or onychoschizia) are findings that should not be overlooked. Treatment of scabies should involve attention to nail treatment, as one prospective study found that about 6% of children with confirmed scabies had nail involvement.

Chinazzo M, Desoubeaux G, Leducq S, et al. Prevalence of nail scabies: a French prospective multicenter study. *J Pediatr.* 2018;197: 154–157.

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111. Of scabies and bed bugs and lice (oh my!), which is most likely to have “hitchhiked” and survived in your luggage after a long trip home?

Bed bugs are the most likely culprit. They have been reported to have spread between dwellings by crawling onto objects, such as luggage. They are also hardier. At room temperature, an adult bedbug can survive 2 to 3 months without a blood meal. Since it is cold-blooded, it can survive without feeding for up to 1 year in chillier climates. Conversely, a scabies mite usually doesn’t survive >3 days without skin contact. Away from the scalp, head lice usually don’t survive >2 days at room temperature.

112. In what condition is the “breakfast, lunch, and dinner” sign noted?

This is a reference to the tendency of a crawling insect to leave a line of bites in its path as it feeds. A typical appearance is a series of linear pink or urticarial papules, each with a central pinpoint punctum, that occur in response to the bite of a **bed bug** *(Cimex lectularius)* or another crawling insect (Fig. 4.16).

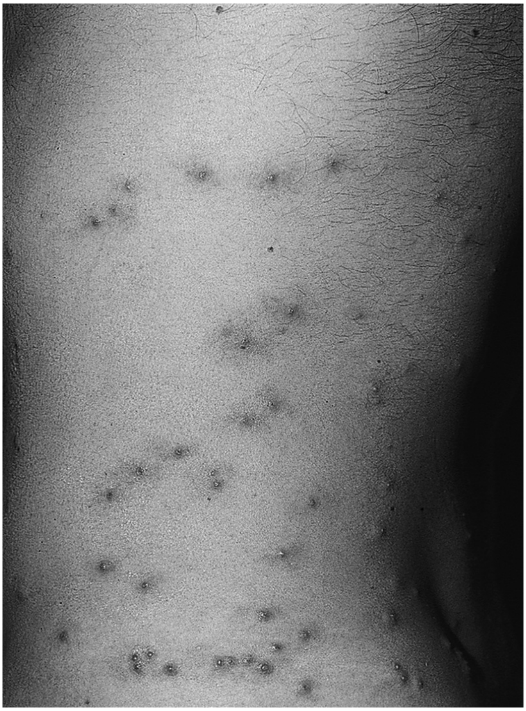

Fig. 4.16 Bed bug bites with erythematous wheals or papules that may itch. They frequently attack exposed areas, especially at night. (Callen JP, Greer KE, Paller AS, et al. *Color Atlas of Dermatology*. 2nd ed. Philadelphia, PA: WB Saunders; 2000:67.)

113. Will getting a new mattress ensure that the bed bugs won’t bite?

No, infestations are not limited to the mattress. Other furniture, clutter in the room, and cracks and crevices in the wall or floor may also harbor bed bugs. They are then attracted to the warm moist carbon dioxide around the sleeping child in the dark of night.

NEONATAL CONDITIONS

114. What are the most common birthmarks?

- **Salmon patches** (nevus simplex, vascular stains) are faint, pink-red, macular patches composed of distended dermal capillaries that are found on the glabella, eyelids, and the nape of the neck. They are seen in 70% of white infants and 60% of black infants. Although they usually fade, they may persist indefinitely, becoming more prominent during crying.
- **Mongolian spots** (dermal melanosis) are blue-black macules that are found on the lumbosacral area and occasionally on shoulders and backs. They are seen in 80% to 90% of babies with darker skin types but ≤10% of white fair-skinned infants. Most of these spots fade by 2 years of age and disappear by age 10.

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115. What types of birthmarks might not be present at birth?

Many congenital features can take several weeks to months to become visible, including:

- **Infantile hemangiomas**, which might show a precursor at birth but will grow and become more prominent in the following weeks
- **Other vascular malformations**, including microcystic lymphatic malformations, venous malformations located in the deeper tissues, and arteriovenous malformations
- **Thyroglossal duct cysts, dermoid cysts**, and **branchial cleft** cysts are also often not visible in the newborn period and become apparent as children mature.

116. What distinguishes common neonatal papular lesions?

See Table 4.3.

Table 4.3 Common Neonatal Papular Lesions

Characteristics	Neonatal cephalic pustulosis	Milia	Erythema toxicum
Distribution	Face	Face and other areas	Face, trunk, and extremities
Appearance	Papule or pustule	Yellow or white papule	Yellow or white papule
Erythematous	Yes	No	Yes
Contents on smear	PMNs	Keratin + sebaceous material	Eosinophils
Incidence	Occasional	40%-50% of term infants	30%-50% of term infants
Course	Last several months	Disappear over weeks to months	Disappear in 2 weeks

PMNs, Polymorphonuclear cells.

117. What is the differential diagnosis of vesicles or pustules in the newborn?

It is very important to rule out infectious etiologies, because some may be life threatening. The purulent material should be evaluated with a Gram stain, potassium hydroxide (KOH), Tzanck preparation, and bacterial and viral cultures. A Wright stain will reveal the presence of neutrophils or eosinophils. See Table 4.4.

Table 4.4 Differential Diagnosis of Vesicles and Pustules in the Newborn

NONINFECTIOUS	INFECTIOUS
Miliaria	Candidiasis
Erythema toxicum	Staphylococcal folliculitis/impetigo
Transient neonatal pustular melanosis	Herpes simplex
Neonatal cephalic pustulosis (neonatal acne)	Congenital syphilis
Infantile acropustulosis	Varicella
Incontinentia pigmenti	Bacterial sepsis
Langerhans cell histiocytosis	Scabies

Adapted from: Frieden IJ, Howard R. Vesicles, pustules, bullae, erosions and ulcerations. In Eichenfield LF, Frieden IJ, Esterly NB, eds. *Textbook of Neonatal Dermatology.* 2nd. Philadelphia, PA: W.B. Saunders; 2008:131–158.

118. What is the medical significance of cutis marmorata?

Cutis marmorata is the bluish mottling of the skin often seen in infants and young children who have been exposed to low temperatures or chilling. The reticulated marbling effect is the result of dilated capillaries and venules causing darkened areas on the skin that disappear with warming. Cutis marmorata is of no medical significance and does not require treatment. In contrast, *persistent* cutis marmorata is associated with trisomy 21, trisomy 18, and Cornelia de Lange syndromes. There is also a congenital vascular anomaly called *cutis marmorata telangiectatic congenita* (CMTC) that has persistent purple reticulate mottling of the skin. In addition, capillary malformations (port wine stains) may have a reticulated appearance and be mistaken for cutis marmorata.

119. A healthy infant with scattered reddish nodules on the back skin most likely has what condition?

Subcutaneous fat necrosis consists of sharply circumscribed, indurated, nodular lesions usually seen in healthy, term newborns and infants during the first few days to weeks of life. The stony hard areas of panniculitis are reddish to violaceous in color and are most often found on the cheeks, back, buttocks, arms, and thighs. Most lesions are self-limiting and require no therapy. However, occasionally they may extensively calcify and spontaneously drain with subsequent scarring. Remember that significant hypercalcemia may be present in a small number of patients. Therefore a serum calcium level should be ordered whenever the disorder is suspected. It should be rechecked periodically until the condition resolves and for several months thereafter.

Stefanko NS, Drolet BA. Subcutaneous fat necrosis of the newborn and associated hypercalcemia: a systematic review of the literature. *Pediatr Dermatol.* 2019;36(1): 24–30.

120. What should the family of a newborn with a yellow, hairless patch with a cobblestone texture be advised to do?

The lesion is likely a **nevus sebaceous**. This hamartomatous neoplasm usually presents as a yellow-pink hairless plaque on the scalp or face at the time of birth (Fig. 4.17) and is composed primarily of malformed sebaceous glands. Under the influence of androgens at puberty, the glands may hypertrophy and lead to the development of other neoplasms, most often benign adnexal tumors. The exact risk for basal cell carcinoma development is controversial, but generally low. Some experts advise excision during the preteen, prepubertal years. Careful monitoring of the lesion for new growths or nonhealing ulcerations at all ages is advised, especially during adolescence.

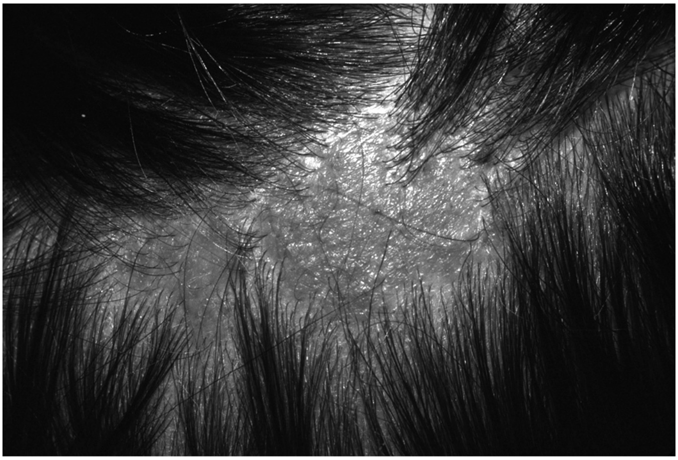

Fig. 4.17 Orange-yellow nevus sebaceous of the scalp. (From Kleigman RM, Stanton BF, Schor NF, et al. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:2235.)

121. What is the appearance of aplasia cutis congenita?

Aplasia cutis congenita (congenital absence of the skin) presents on the scalp as solitary or multiple well-demarcated ulcerations or atrophic scars. Of variable depth, the lesions may be limited to the epidermis and upper dermis or occasionally extend into the skull and dura (Fig. 4.18). When a "hair collar" is present, an underlying connection, such as a dermoid sinus tract with the CNS, must be considered. Lesions that are large, stellate in shape, midline, or associated with additional skin findings such as a capillary malformation are also more likely to be associated with underlying dysraphism. Although most children with this lesion are otherwise normal without associated anomalies, other associations include epidermolysis bullosa (EB), placental infarcts, teratogens, sebaceous nevi, and limb anomalies. Aplasia cutis is a feature of trisomy 13, chromosome 4p syndrome, oculocerebrocutaneous (Delleman Oorthuys) syndrome and Adams-Oliver syndrome.

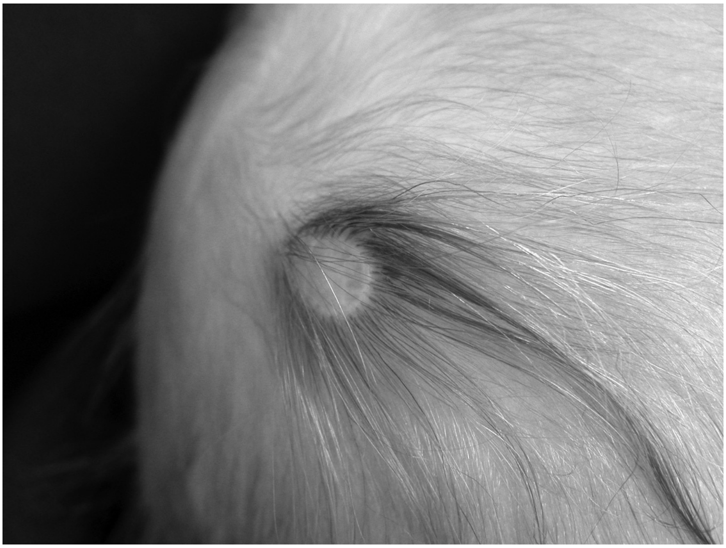

Fig. 4.18 Healed aplasia cutis congenita with “hair collar sign.” (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis*. 5th ed. Philadelphia, PA: Mosby Elsevier; 2011:342.)

122. Describe the appearance and distribution of transient neonatal pustular melanosis

Consisting of small vesicopustular lesions 2 to 4 mm in size, transient pustular melanosis occurs in almost 5% of black and $<$1% of white newborns. It may be present at birth or appear shortly after birth. The lesions most often cluster on the neck, chin, palms, and soles, although they may occur on the face and trunk. The pustules rupture easily and progress to brown, pigmented macules with a fine collarette of scale (Fig. 4.19). Microscopic examination of the contents of the pustules reveals neutrophils with no organisms. There are no associated systemic manifestations, and the eruption is self-limited, although the hyperpigmentation may last for months.

Chadha A, Jahnke M. Common neonatal rashes. *Pediatr Ann.* 2019;8(1):e16–e22.

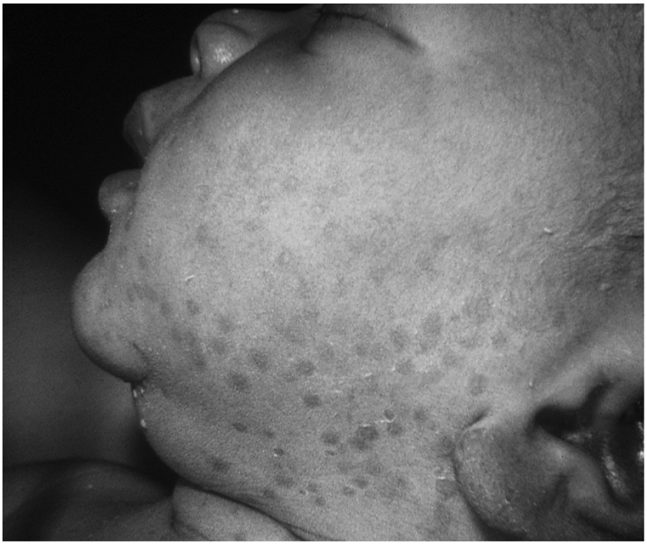

Fig. 4.19 Pustular melanosis. (From Clark DA. *Atlas of Neonatology*. Philadelphia, PA: W.B. Saunders; 2000:261.)

123. Is erythema toxicum neonatorum really toxic?

Not in the least. *Erythema toxicum* is a common eruption composed of erythematous macules, papules, and pustules that occur in newborns, usually during the first few days of life. The lesions may start as irregular, blotchy, red macules, varying in size from millimeters to several centimeters. They often develop into 1- to 3-mm yellow-white papules and pustules on an erythematous base, giving a “flea-bitten” appearance. They occur all over the body except on the palms and soles, which are spared because the lesions occur in pilosebaceous follicles, which are absent on the palmar and plantar surfaces. The rash is less common in premature infants, with incidence proportional to gestational age and peaking at 41 to 42 weeks. Although it may be seen at birth, it is most common during the first 3 to 4 days of life and is occasionally noted as late as 10 days of life. Erythema toxicum usually lasts 5 to 7 days and heals without pigmentation. Other than the rash, the newborn appears healthy.

124. What is the technical term for “prickly heat”?

The scientific name for this condition is *miliaria rubra*. It is due to sweat retention, and its clinical morphology is determined by the level at which sweat is trapped. Sweat trapped at a superficial level produces clear vesicles without surrounding erythema (sudamina or crystallina). Miliaria rubra (prickly heat, erythematous papules, vesicles, papulovesicles) is produced by sweat trapped at a deeper level. Pustular lesions (miliaria pustulosa) and even abscesses (miliaria profunda) are produced with sweat retention at the deepest of levels (infants rarely develop these types). With the advent of air conditioning, miliaria rarely occurs in newborn nurseries.

PAPULOSQUAMOUS DISORDERS

125. What diseases are associated with the Koebner reaction?

Koebnerization is a response to local injury whereby skin lesions are found at the sites of trauma (e.g., linear lesions at the sites of scratching). This is seen in patients with psoriasis (Fig. 4.20), as well as those with other conditions, including lichen planus, lichen niditus, and flat warts.

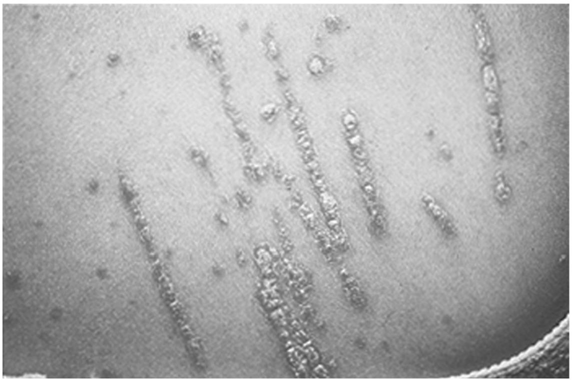

Fig. 4.20 Koebner phenomenon in psoriasis with linear plaques at site of excoriations. (From Cohen BA. *Pediatric Dermatology.* 2nd ed. St. Louis, MO: Mosby; 1999:63.)

126. What is the typical pattern of lesions in childhood psoriasis?

Psoriasis presents as well-circumscribed, erythematous plaques with overlying white scale in children and adults. Common sites include the scalp, elbows, knees (Fig. 4.21), sacrum, and genitalia. Psoriasis may also present with guttate (droplike) lesions over the trunk and extremities. These children may have group A beta-hemolytic streptococcus infection as an underlying precipitating factor.

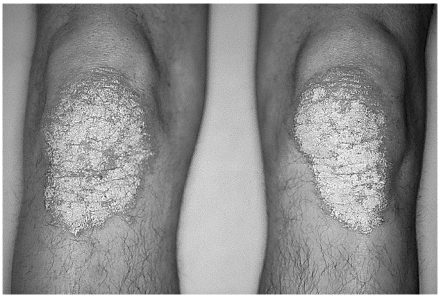

Fig. 4.21 Plaques of psoriasis on the knees. (From Gawkrodger DJ. *Dermatology: An Illustrated Colour Text*. 3rd ed. London: Churchill Livingstone; 2002:27.)

127. What percentage of children with psoriasis have nail involvement?

Nail changes, most commonly pitting, may be the only manifestation of psoriasis (Fig. 4.22). The reported incidence of nail pitting in children with psoriasis is as high as 40%. In a recent study, boys were found to have nail involvement more often than girls. Other nail changes include onycholysis (separation of the nail plate from nail bed at the distal margin) and thickening of the nail plate, often with white-yellow discoloration.

Mercy K, Kwasny M, Cordoro KM, et al. Clinical manifestations of pediatric psoriasis: results of a multicenter study in the United States. *Pediatr Dermatol.* 2013;30(4):424–428.

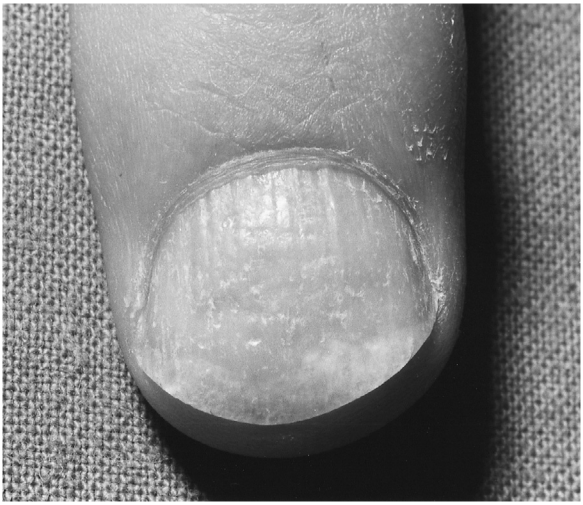

Fig. 4.22 Nail pitting associated with psoriasis. (From Goldbloom RB. *Pediatric Clinical Skills*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011:228.)

128. A skin scale that easily bleeds on removal is characteristic of what condition?

The appearance of punctate bleeding points after removal of a scale is known as the *Auspitz sign*. It is seen primarily in **psoriasis** and is related to the rupture of capillaries high in the papillary dermis, near the surface of the skin.

129. How is the increased prevalence of childhood obesity associated with psoriasis?

Children with psoriasis have a higher likelihood of developing obesity. Adolescent patients with psoriasis have higher blood lipids, with obesity being a stronger independent risk factor than psoriasis. This highlights the importance of screening children with psoriasis, especially those who are overweight, for cardiovascular disease risk factors and other comorbidities.

Tollefson MM, Van Houten HK, Asante D, et al. Association of psoriasis with comorbidity development in children with psoriasis. *JAMA Dermatol.* 2018;154(3):286–292.

130. What are treatment modalities for psoriasis?

Various therapies have been used to treat psoriasis. The choice of treatment will depend on the extent of involvement, previous treatments, and age of the patient. Topical treatments include topical corticosteroids, calcipotriene (a vitamin D analog), retinoids, and tar. Other treatment modalities include ultraviolet B (UVB) (typically narrow-band UVB) phototherapy and, rarely, systemic retinoids and methotrexate. Biologic agents such as etanercept have been used to treat widespread moderate to severe psoriasis in pediatric patients.

Eichenfield LF, Paller AS, Tom WL, et al. Pediatric psoriasis: evolving perspectives. *Pediatr Dermatol.* 2018;35(2):170–181.
Shah KN. Diagnosis and treatment of pediatric psoriasis. *Am J Clin Dermatol.* 2013;14(3):195–213.

131. What are the eight Ps of lichen planus?

- **Papules**: usually 2 to 6 mm in diameter; often seen in a linear pattern as a result of the Koebner phenomenon (see question 125)
- **Plaques**: commonly generated from a confluence of papules with exaggerated surface markings of the overlying skin (Wickham striae)
- **Planar**: individual lesions, usually flat-topped
- **Purple**: distinctly violaceous
- **Pruritus**: often intensely itchy
- **Polygonal**: borders of papules are often angulated
- **Penis**: common site of involvement in children
- **Persistent**: chronic, with remissions and exacerbations for up to 18 months

132. How is pityriasis rosea distinguished from secondary syphilis?

The distinction is often made with difficulty because both are primarily papulosquamous rashes. *Pityriasis rosea* classically consists of oval lesions that organize in parallel fashion on the trunk (the “Christmas tree” distribution) and are preceded in 40% to 80% of cases by a large annular erythematous lesion (herald patch). *Secondary syphilis* lesions occur 3 to 6 weeks after the chancre, and compared with pityriasis rosea, they may have more involvement of the palms, soles, and mucous membranes and accompanying lymphadenopathy. However, because atypical presentations are common, testing for syphilis should be performed in any sexually active individual who is diagnosed with pityriasis rosea.

133. What is the treatment for pityriasis rosea?

Pityriasis rosea is a self-limited condition that usually resolves in 6 to 12 weeks. Therefore treatment is often not required, unless there is significant pruritus or cosmetic disfigurement. A wide range of treatments are reported. Topical corticosteroids may help reduce pruritus, but they do not alter the course of the disease. UVB phototherapy results in clinical improvement in some individuals, and there are a few reports to support the use of oral erythromycin or acyclovir to shorten the course. However, overall evidence supporting the use of these therapies is lacking.

Villalon-Gomez JM. Pityriasis rosea: diagnosis and treatment. *Am Fam Physician.* 2018;97(1):38–44.

134. What is the likely diagnosis for a 5-year-old who presents with a linear array of recently acquired pink to hypopigmented papules on the leg?

Although the differential diagnosis may be broad, a common cause of this type of eruption is **lichen striatus** (Fig. 4.23), which consists of linear collections of small, erythematous, flat-topped papules, most commonly seen

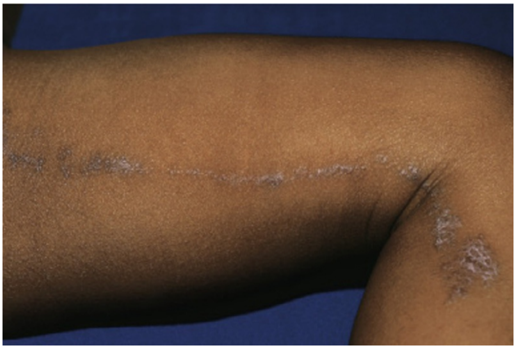

Fig. 4.23 Lichen striatus. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*. 5th ed. Philadelphia, PA: Elsevier; 2016:61.)

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on the extremities. This eruption is generally asymptomatic, does not require treatment, and lasts from weeks to a few years. Light spots following the acute rash may persist for longer. This eruption follows the lines of Blaschko, which mark embryonic cell migration lines.

Peramiquel L, Baselga E, Dalmau J, et al. Lichen striatus: clinical and epidemiological review of 23 cases. *Eur J Pediatr.* 2006;165(4):267–269.

135. A 5-year-old who presents with a several-week history of numerous small, oval, pink, scaly papules, some with crusting and central necrosis, has what likely diagnosis?

While at first glance you might consider chicken pox (varicella) or even pityriasis rosea, this child likely has **pityriasis lichenoides et varioliform acuta** (PLEVA). This idiopathic eruption can resemble the necrotic lesions of varicella in the acute phase. In some children, the eruption can last for months to years, termed *pityriasis lichenoides chronica (PLC),* often leaving hypopigmented macules at the sites of prior lesions. There is concern about potential transformation to cutaneous lymphoma, so patients should be followed long-term. Treatment options include oral antibiotics with anti-inflammatory properties, such as erythromycin or doxycycline, in the appropriate age groups. In some cases, narrow-band UVB phototherapy is utilized. These lesions are typically nonresponsive to topical steroids. Successful use of topical calcineurin inhibitors has been reported.

Geller L, Antonov NK, Lauren CT, Morel KD, Garzon MC. Pityriasis lichenoides in childhood: review of clinical presentation and treatment options. *Pediatr Dermatol.* 2015;32(5):579–592.

PHOTODERMATOLOGY

136. Why is limiting excessive sun exposure in children important?

Years of unprotected sun exposure will lead to freckling, wrinkling, and increased risk for developing skin cancer, including melanoma. In an era of rising rates of melanoma and squamous and basal cell carcinomas, the use of sun-protection strategies during the pediatric years could lower the risk for skin cancer in adulthood.

137. Why should indoor tanning be addressed and discouraged in children?

Indoor tanning is associated with an increased risk for melanoma in adulthood. One study found that indoor tanning before the age of 35 years increases the risk for melanoma by 59%. Historically, many indoor tanning users start early: 53% began tanning before age 21, with approximately one-third starting before 18. Many, but not all, states now have legislation restricting tanning bed use among minors.

Watson M, Shoemaker M, Baker K. Indoor tanning initiation among tanners in the United States. *JAMA Dermatol.* 2017;153(5): 470–472.

138. What are good strategies for protection against sun exposure?

- Seek shade when possible and remember that the sun’s rays are strongest between 10 AM and 4 PM.
- Remember that water, snow, and sand reflect the sun’s rays and may increase your chance of sunburn.
- Wear protective clothing, hats, and sunglasses.
- Apply sunscreen at least 30 minutes before sun exposure.
- Use a broad-spectrum sunscreen with a sun protection factor (SPF) of 30 or higher.
- Apply liberal amounts of sunscreen: about 1 oz (shot glass size or 30 mL) is enough to cover the exposed skin areas of an average sized adult; 15 mL is typically required for a 7-year-old child.
- Use a water-resistant sunscreen, and reapply sunscreen every 80 minutes during water-based activities or when sweating.
- Wear lip protection that contains sunscreen.

American Academy of Dermatology. www.aad.org/public/kids/skin/taking-care-of-your-skin/protect-your-skin-from-the-sun. Accessed June 16, 2019.

139. How is the SPF of a sunscreen determined?

SPF is the level of effectiveness of a sunscreen’s ability to protect primarily against UVB light. It is not a measurement of ultraviolet A (UVA) light protection. The SPF rating is a ratio derived from the minimal dose of solar radiation needed to produce perceptible erythema on sunscreen-protected skin compared with unprotected skin. An SPF of 50 will allow one-fiftieth of UVB to produce perceptible erythema, so it filters 98%.

140. What should parents look for in a sunscreen label?

The FDA has mandated updated language regarding sunscreen labeling. Parents should look for a sunscreen that is described as *broad spectrum,* which indicates that it will be effective against both UVA and UVB rays.

A product with an *SPF of 30 to 50* is preferred. Parents should look for *water-resistant sunscreen*; however, 80 minutes is the maximum time that a sunscreen will remain on the skin during water-based activities or with sweating. Advice should also include physical protection, including wearing sun-protective clothing, hats, and sunglasses. Of note, a vitamin D supplement should be considered when practicing cautious sun protection, especially if insufficient vitamin D is being derived from a fortified diet.

141. What is the SPF of a suntan?

A suntan provides SPF protection of **4 or less.** It is not a good way to protect against the sun.

American Academy of Dermatology. www.aad.org/education/basic-derm-curriculum/suggested-order-of-modules/sun-protection. Accessed June 16, 2019.

142. What is the difference between physical and chemical sunscreens?

Zinc oxide and titanium dioxide are *physical sunscreens,* which reside on the surface of the skin and act as shields deflecting UV rays. As a result, they often are characterized by a whitish film. Physical sunscreens are often preferred for people with sensitive skin. *Chemical sunscreens* work like a sponge, absorbing the sun's radiation and dissipating the energy in the form of heat.

DeLeo VA. Sunscreens and photoprotection. In Bolognia JL, Schaffer JV, Cerroni L, Callen JP, eds. *Dermatology.* 4th ed. Edinburgh: Elsevier; 2018:2310–2317.

143. How protective is a beach umbrella?

On a sunny day, beach umbrellas alone provide only limited sun protection. The umbrella fabric's sun protection ability will vary depending upon the fabric's composition and placement relative to the rays. In addition, the umbrella provides limited protection because UV rays from the sun are reflected *under* the umbrella from the surfaces of the sand, sky, and water.

Ou-Yang H, Jiang Li, Meyer K, et al. Sun protection by beach umbrella vs sunscreen with a high sun protection factor: a randomized clinical trial. *JAMA Dermatol.* 2017;153(3):304–308.

144. Why can a hot day at the beach lead to recurrence of "cold sores"?

Reactivation of labial herpes simplex virus 1 (HSV-1) infections (cold sores) has been described after sun exposure at the beach or while skiing at high altitudes. The reactivation is felt to be secondary to the immunosuppressive effects of UV radiation, which leads to "photo-immunosuppression" and reactivation of HSV-1 in the neural ganglia.

DeLeo VA. Sunscreens and photoprotection. In Bolognia JL, Schaffer JV, Cerroni L, Callen JP, eds. *Dermatology.* 4th ed. Edinburgh: Elsevier; 2018:2310–2317.

Ichihashi M, Nagai H, Matsunaga K. Sunlight is an important causative factor of recurrent herpes simplex. *Cutis.* 2004; 74(5 Suppl):14–18.

145. Should sunscreens be avoided in young infants?

This is controversial in infants under 6 months of age. There are concerns that the skin of infants <6 months of age has different absorptive characteristics and that biologic systems that metabolize and excrete drugs may not be fully developed. Therefore clothing protection and sun protective behaviors are advised for children <6 months of age. Physical protection (e.g., clothing, hats, shade, sunglasses) and avoidance of sun during peak hours are ideal, but the skin of an infant <6 months is not adequately protected; it may be reasonable to apply sunscreen to small areas, such as the face and the back of the hands.

American Academy of Pediatrics. www.healthychildren.org/English/ages-stages/baby/bathing-skin-care/Pages/Baby-Sunburn-Prevention.aspx. Accessed June 27, 2019.

Long M. Sun exposure. *Pediatr Rev.* 2017;38(9):446–447.

146. Which "lime" disease is not transmitted by ticks?

Limes contain psoralens that react with UV light and that can produce erythema, vesicles, and/or hyperpigmentation on areas of the skin that have come in contact with lime juice. This is known as

phytophotodermatitis and is seen with other psoralen-containing plants, such as celery and figs. Additionally, berloque dermatitis (berloque is French for “pendant,” which some lesions can resemble) is an irregularly patterned hyperpigmentation of the neck due to photosensitization by furocoumarins (i.e., psoralens) in perfumes. It is caused by fragrances that contain bergamot oil, an extract from the peel of a type of orange that is grown in southern France and Italy. Bergamot oil contains 5-methoxypsoralen, which enhances the erythematous and pigmentary response of UVA light.

147. When should “photosensitivity” be suspected?

Most people will develop a sunburn if they are exposed to sun for a prolonged period without adequate sun protection. *Photosensitivity* is an abnormal reaction to limited sun exposure and should be suspected when a sunburn, an itchy rash, or swelling arises after limited exposure. Photosensitivity conditions are typically found on sun-exposed areas of the body and may leave scarring. Conditions associated with marked photosensitivity are noted in Table 4.5.

Chantorn R, Lim HW, Shwayder TA. Photosensitivity disorders in children: part I. *J Am Acad Dermatol.* 2012;67(6):1093.e1–e18.
Chantorn R, Lim HW, Shwayder TA. Photosensitivity disorders in children: part II. *J Am Acad Dermatol.* 2012;67(6):1113.e1–e15.

Table 4.5 Conditions Associated With Photosensitivity

Systemic disease	Lupus erythematosus, juvenile dermatomyositis
Inherited disorders	Porphyrias, xeroderma pigmentosum, Bloom syndrome, Rothmund-Thomson syndrome, Hartnup disorder
Exogenous agents	Drugs (e.g., tetracyclines, thiazides), photoallergic contact dermatitis (associated with perfumes and para-aminobenzoic acid esters)
Idiopathic disorders	Polymorphous light eruption, solar urticaria, actinic prurigo, hydroa vacciniforme

148. What is the appearance of polymorphous light eruption?

The most common pediatric photodermatosis, *polymorphous light eruption* (PMLE), is characterized by itchy red papules, plaques, or papulovesicles that appear several hours to days after UV light exposure. It can be diagnosed by phototesting (i.e., the induction of lesions by intentional UV light exposure) and by skin biopsy. It is usually suggested by the classic history and the exclusion of other photosensitivity diseases.

Gruber-Wackernagel A, Byrne SN, Wolf P. Polymorphous light eruption: clinical aspects and pathogenesis. *Dermatol Clin.* 2014;32(3):315–334.

PIGMENTATION DISORDERS

149. What disorders of childhood are associated with areas of hypopigmentation?

Hypopigmentation is caused by a decrease—not a total absence—of pigmentation or melanin. Conditions that feature hypopigmented lesions include **tuberous sclerosis**, **tinea versicolor**, **pityriasis alba**, **nevus depigmentosus**, **hypomelanosis of Ito**, **leprosy**, and **postinflammatory hypopigmentation**.

150. What treatments are available for vitiligo?

Vitiligo is a disorder of depigmentation (total absence of pigmentation with sharp demarcations; Fig. 4.24). The etiology is unknown, but is thought to be polygenic autoimmune in nature. There are rare associations with other autoimmune conditions, including autoimmune thyroiditis and juvenile-onset diabetes. Potent topical steroids have been used for localized areas. Off-label topical tacrolimus ointment has been used with some success to treat facial vitiligo in children. UV light therapy has been employed for some children with severe, extensive disease. Excimer laser (308 nm) has been instituted as an effective treatment for focal disease. Dyes (including self-tanning agents) and coverage cosmetics are often helpful for camouflaging skin lesions.

Ezzedine K, Silverberg N. A practical approach to the diagnosis and treatment of vitiligo in children. *Pediatrics.* 2016;138(1):e20154126.

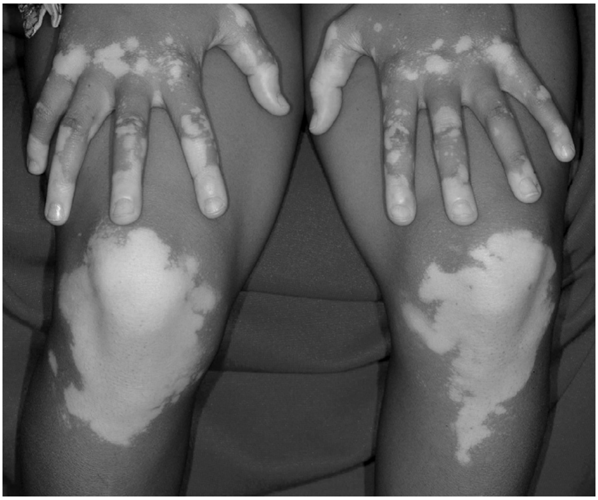

Fig. 4.24 Vitiligo. Note well-demarcated areas of total depigmentation. (From White GM, Cox NH. *Diseases of the Skin: A Color Atlas and Text*. London, UK: Mosby; 2002:286.)

151. Which patients with vitiligo warrant additional laboratory testing?

It depends on the pattern of the vitiligo and the history. Patients with *segmental vitiligo* (a unilateral or bandlike area of involvement) do not require a systemic workup, unless they have a preexisting autoimmune condition or additional features that are suggestive of autoimmune disease. Patient with *nonsegmental vitiligo* (multiple focal areas of involvement) should be assessed for other signs of autoimmune disease. In particular, a thorough family history along with screening laboratory studies are recommended, including complete blood count, metabolic panel, thyroid function tests, and thyroid autoantibodies (i.e., antithyroid peroxidase and anti thyroglobulin). Vitiligo is associated with autoimmune endocrine disorders. Vitamin D deficiency is common, so 25-hydroxy vitamin D levels should be measured. Antinuclear antibody (ANA) screening is also advised before beginning any phototherapy.

Ezzedine K, Silverberg N. A practical approach to the diagnosis and treatment of vitiligo in children. *Pediatrics.* 2016;138(1):e20154126.

152. Why are Spitz nevi and malignant melanoma often confused?

A *Spitz nevus* can appear suddenly and grow rapidly. Histologically, it has many features that can be mistaken for malignancy. It actually was previously referred to as *benign juvenile melanoma*. “Benign” is the key word for this red to brown, dome-shaped papule, which usually appears on the face or extremity (Fig. 4.25). It can be

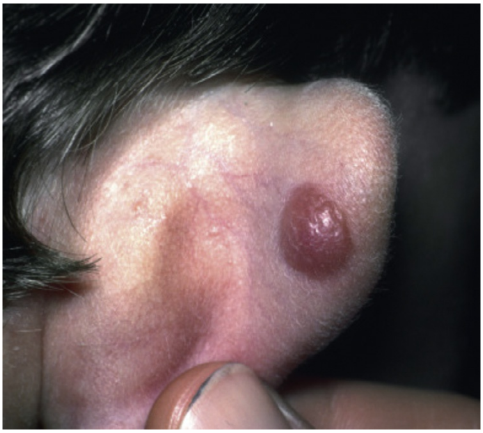

Fig. 4.25 Spitz nevus. (From James WD, Elston DM, Treat JR, et al, eds. *Andrews' Diseases of the Skin*. 13th ed. Philadelphia, PA: Elsevier; 2020:391.)

blue-black in color, which adds to the clinical concern. Clinicopathologic correlation is the key to making this diagnosis. It is essential that an experienced pathologist interpret the biopsy when a Spitz nevus is suspected. Melanoma in childhood has been misdiagnosed as Spitz nevi, and conversely, Spitz nevi have been misdiagnosed as melanoma.

Dika E, Ravaioli GM, Fanti PA, et al. Spitz nevi and other Spitzoid neoplasms in children: overview of incidence data and diagnostic criteria. *Pediatr Dermatol.* 2017;34(1):25–32.

153. How common are congenital melanocytic nevi?

One to two percent of children have a congenital melanocytic nevus (also called *moles*) and are often born with precursor lesions, which may resemble a café au lait macule.

154. Which congenital melanocytic nevi are most worrisome?

Large, giant, or multiple nevi are most concerning. Congenital nevi are categorized based on the size of the lesion: small (<1.5 cm), medium (1.5 cm to 20 cm), large (>20 cm), and giant (>40 cm). Numerous scattered smaller lesions, which may become visible after birth, are known as *satellite nevi.* Larger congenital nevi and those with multiple satellite nevi are typically associated with a risk for neurocutaneous melanosis (NCM) or congenital melanocytic nevus syndrome (CMN syndrome). Abnormalities of the CNS, including intraparenchymal melanin deposits and structural brain abnormalities seen in CMN syndrome, are best diagnosed by magnetic resonance imaging (MRI) before myelinization. Melanoma risk is variably reported in this group, typically <10%, and is highest in children with multiple satellites and those children with abnormal brain MRIs. Lifelong monitoring by a dermatologist is recommended to monitor for development of melanoma. Management of skin lesions is individualized.

Kinsler VA, O'Hare P, Bulstrode N, et al. Melanoma in congenital melanocytic naevi. *Br J Dermatol.* 2017;176(5):1131–114.
Waelchli R, Aylett SE, Atherton D, et al. Classification of neurological abnormalities in children with congenital melanocytic naevus syndrome identifies magnetic resonance imaging as the best predictor of clinical outcome. *Br J Dermatol.* 2015;173(3):739–750.

155. How do the ABCs of pediatric melanoma differ from adult melanoma?

The conventional melanoma detection criteria in adults are based on the "**ABCDE**" rules, which stand for **A**symmetry, **B**order irregularity, **C**olor variegation, **D**iameter >6 mm, and **E**volution. In a recent retrospective review of pediatric melanoma, **A**melanosis, **B**leeding, "**B**umps," uniform **C**olor, variable **D**iameter, and **De** novo development were proposed as additional descriptors for detecting melanoma in the pediatric population.

Cordoro KM, Gupta D, Frieden IJ, et al. Pediatric melanoma: Results of a large cohort study and proposal for modified ABCD detection criteria for children. *J Am Acad Dermatol.* 2013;68(6):913–925.

156. What conditions are associated with congenital depigmentation of the skin?

Congenital depigmentation, or albinism, constitutes a number of genetically inherited syndromes that are characterized by disorders of melanin synthesis and that may affect the skin, hair, and eyes. **Generalized (oculocutaneous) albinism** is often complicated by ocular abnormalities, including visual impairment, photophobia, and nystagmus. **Piebaldism** is a distinct form of congenital depigmentation that affects segments of skin. Patients with this condition often have a forelock of white hair, which is caused by a genetic mutation that differs from generalized albinism. **Localized congenital depigmentation** associated with a white forelock, heterochromia irides, and congenital deafness characterizes Waardenburg syndrome.

157. What is the significance of patterned pigmentation in the skin?

Patterned pigmentation, or pigmentary mosaicism, is characterized by lighter (hypo) or darker (hyper) shades of skin color. This can be a sign of an underlying systemic condition or simply an isolated finding. Patterned pigmentation can be seen in characteristic patterns, including pigmentation that follows the lines of Blaschko (see question 158) or in other patterns such as checkerboard or phylloid (leaf). Focal or limited and unilateral alterations in pigmentation rarely have associated abnormalities. However, more widespread hyperpigmentation or hypopigmentation may be associated with a systemic condition. There is no absolute size or guideline to predict which patients will manifest systemic abnormalities. Consequently, continued monitoring and investigation for neurologic, ocular, cardiac, and musculoskeletal system abnormalities, along with a referral for genetic evaluation, may be necessary depending on the clinical findings and symptoms.

Treat J. Patterned pigmentation in children. *Pediatr Clin North Am.* 2010;57(5):1121–1129.

158. What are Blaschko lines?

Blaschko lines represent the pattern of embryonic migration of the melanocytes and keratinocytes arising from the ectoderm. They are wavy and whorled and are distinct from dermatomes, which represent patterns of sensory innervation. Numerous dermatologic conditions can follow Blaschko lines, including lichen striatus, linear lichen planus, and incontinentia pigmenti (IP). In IP, vesicular, verrucous, hyperpigmented, and finally hypopigmented skin lesions occur along Blaschko lines. IP is associated with neurodevelopmental delays, ocular abnormalities, dental and hair anomalies, and, more rarely, cardiac abnormalities.

159. How can the shape or pattern of café au lait macules provide a clue to a diagnosis?

Café au lait macules, when present in multiple small numbers with smooth borders (six or more, >5 mm in prepubescent children, or >1.5 cm after puberty), are one cutaneous manifestation of neurofibromatosis. A large café au lait macule with "coast of Maine" borders should prompt consideration for McCune Albright syndrome, which is associated with precocious puberty and polyostotic fibrous dysplasia.

VASCULAR BIRTHMARKS

160. How are vascular birthmarks classified?

The updated biologic classification of vascular birthmarks is the most widely accepted classification of vascular birthmarks. It was first proposed in 1982 and has been updated to reflect new knowledge. Three categories of vascular birthmarks are described: **vascular tumors, vascular malformations, and provisionally unclassified lesions**. There are many types of vascular tumors, but infantile hemangiomas are the most common. These demonstrate cellular hyperplasia. Vascular malformations, which are composed of dysplastic, malformed vessels, are categorized on the basis of their flow characteristics and type of anomalous channels. The majority of vascular anomalies seen in childhood fit into these categories.

Vascular tumors (select):

- Infantile hemangioma
- Congenital hemangioma
- Kaposiform hemangioendothelioma
- Tufted angioma
- Pyogenic granuloma

Vascular malformations:

- Capillary malformation (port wine stains, salmon patch)
- Lymphatic malformation (lymphangioma microcystic, macrocystic)
- Venous malformations
- Arteriovenous malformations
- Combined malformations

Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics.* 2015;136(1):e203–e214.

Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children. *Plast Reconstr Surg.* 1982;69(3):412–420.

161. What is the natural history of untreated infantile hemangiomas?

Hemangiomas, or more specifically, infantile hemangiomas, are common benign vascular tumors. They are rarely fully developed at birth, but precursor lesions (an area of pallor, telangiectasia, or "bruiselike" patch) may be detected on close inspection within the first few days of life. They may have superficial and/or deep components. Hemangiomas undergo a growth phase within the first year of life. They mark out their territory early and thereafter may grow in thickness or volume. Growth is nonlinear and often most dramatic in the first few months of life, with many reaching 80% of their maximum size by 3 months of age. The process of involution occurs over several years, with many undergoing significant involution in the first 4 years of life. When involution is complete, there still may be residual skin changes (e.g., skin redundancy, pallor, atrophy, telangiectasia). Management of infantile hemangiomas needs to be individualized because many factors are assessed in the decision to actively treat them.

Luu M, Frieden IJ. Haemangioma: Clinical course, complications and management. *Br J Dermatol.* 2013;169(1):20–30.

162. What are the major goals of the management of infantile hemangiomas?

The decisions regarding which hemangiomas require treatment and the best therapeutic modalities may not always be easy. The major goals of management are as follows:

- Prevent or reverse life- or function-threatening complications.
- Treat ulcerated hemangiomas.
- Prevent permanent disfigurement caused by a rapidly enlarging lesion.
- Minimize psychosocial stress for the family and the patient.
- Avoid overly aggressive procedures that may result in scarring in lesions that have a good likelihood of involuting without significant residual skin changes.

Luu M, Frieden IJ. Haemangioma: clinical course, complications and management. *Br J Dermatol.* 2013;169(1):20–30.

163. What can patterns of hemangiomas on the skin surface tell us?

The characteristics of hemangiomas on the skin surface can provide clues to underlying abnormalities and help predict outcomes. Hemangiomas are described as being superficial when they are located in the upper dermis and present as red papules and plaques (“strawberry”). Deep hemangiomas are located in the deeper dermis and subcutaneous tissue and are often blue-purple in color. Mixed hemangiomas have both superficial and deep components (“iceberg phenomenon”). Hemangiomas are also characterized based on their distribution on the skin surface. Hemangiomas that appear to arise from a single focus are called “localized” or “focal” hemangiomas, and lesions that cover a broad area on the skin surface, which might represent a developmental subunit, are called “segmental.” Multiple focal lesions (multifocal) may herald internal hemangiomas, and segmental hemangiomas may predict involvement with other anatomic and developmental disorders (PHACE and LUMBAR syndromes).

Smith CJF, Friedlander SF, Guma M, et al. Infantile hemangiomas: an updated review on risk factors, pathogenesis and treatment. *Birth Defects Res*. 2017;109(11):809–815.

Haggstrom AN, Lammer EJ, Schneider RA, et al. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics.* 2006;117(3):698–703.

164. Which hemangiomas are especially worrisome?

- **Multiple cutaneous hemangiomas** may be associated with visceral hemangiomas (most commonly liver hemangiomas).
- **Large/bulky hemangiomas** may cause significant disfigurement of underlying structures.
- **Segmental hemangiomas** are associated with PHACE and LUMBAR syndromes. LUMBAR is an acronym to describe hemangiomas on the lower body associated with other anomalies:
    - **L**ower body hemangioma and other cutaneous defects
    - **U**rogenital anomalies
    - **M**yelopathy
    - **B**one deformities
    - **A**norectal malformations, arterial anomalies
    - **R**enal anomalies
- **“Beard” hemangiomas** may be a marker for underlying laryngeal or subglottic hemangiomas that may impair respiratory function.
- **Midline spinal hemangiomas** may be a marker for an underlying spinal cord abnormality.
- **Head and neck hemangiomas**, usually segmental lesions >5 cm in diameter, may be associated with other congenital anomalies, including CNS, cardiac, ocular, and sternal defects (e.g., posterior fossa malformation, hemangioma, arterial abnormalities, coarctation, eye abnormalities, sternal defects [PHACE(S)] syndrome).
- **Vulnerable anatomic locations** impair vital functions and cause disfigurement (e.g., periocular, neck, lip, nasal tip).
- **Ulcerated hemangiomas** increase the risk for superinfection and can bleed, cause pain, and lead to scarring.

Haggstrom AN, Drolet BA, Baselga E, et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics.* 2006;118(3):882–887.

165. When is treatment indicated for infantile hemangiomas?

- Lesions that interfere with normal physiologic functioning (i.e., breathing, hearing, eating, vision), especially periocular hemangiomas (to prevent amblyopia)
- Recurrent bleeding, ulceration, or infection
- A rapidly growing lesion that distorts facial features or has the potential to result in a residual lesion that will cause disfigurement

A hemangioma severity scale has been developed and validated. Studies suggest that it may assist as a triage tool to facilitate decision-making about initiating oral propranolol.

Moyakine AV, Herwegen B, van der Vleuten CJM. Use of the Hemangioma Severity Scale to facilitate treatment decisions for infantile hemangiomas. *J Am Acad Dermatol.* 2017;77(5):868–873.

Luu M, Frieden IJ. Haemangioma: clinical course, complications and management. *Br J Dermatol.* 2013;169(1):20–30.

Haggstrom AN, Beaumont JL, Lai JS, et al. Measuring the severity of infantile hemangiomas: instrument development and reliability. *Arch Dermatol.* 2012;148(2):197–202.

166. Are there characteristics of hemangiomas that might predict the likelihood of a residual lesion if left untreated?

Hemangiomas that undergo *ulceration* may leave scars with textural changes. If ulceration occurs within a hemangioma on hair-bearing areas such as the scalp, hair growth may be affected. Hemangiomas that contain a *thicker superficial component with an abrupt border* and a *cobblestoned surface* are more likely to leave eventual redundant skin changes than those with a smooth surface or border with a gentle slope.

Baselga E, Roe E, Coulie J, et al. Risk factors for degree and type of sequelae after involution of untreated hemangiomas of infancy. *JAMA Dermatol.* 2016;152(11):1239–1243.

167. What are the most commonly used treatments for problematic infantile hemangiomas?

In most cases, topical treatments are used for smaller superficial lesions that do not have a significant deep component; systemic medications are used for larger, deeper infantile hemangiomas; those with an aggressive growth pattern; or those that are function threatening or cosmetically disfiguring.

- **Oral propranolol** was first reported to be efficacious for halting the proliferation and speeding the regression of infantile hemangiomas in 2008. In most cases, it has become first-line therapy for problematic hemangiomas. In March 2014, a specific formulation of oral propranolol received FDA approval for treatment of infants >5 weeks with problematic infantile hemangiomas.
- **Topical timolol–gel forming solution**, an ophthalmologic preparation, has been reported to be effective for the treatment of small, thin, superficial hemangiomas; however, its use remains off-label and is limited to small surface areas to reduce the risk for complications from systemic absorption.
- **Pulsed dye laser** may be used with other modalities, but is usually of little benefit in situations when systemic treatment with propranolol is indicated. Limited penetration restricts its use to superficial lesions.
- **Surgical excision** is most commonly used to manage the residual lesions of hemangiomas. Facial lesions that leave a significant residual lesion are often managed around age 3 years before the child starts preschool.
- **Corticosteroids (oral, intralesional, and topical)** used to be mainstays of treatment for hemangiomas. However, their use has been largely supplanted by beta blockers.

Padia R, Bly R, Bull C, et al. Medical management of vascular anomalies. *Curr Treat Options Pediatr.* 2018;4(2):221–236.

Hagen R, Ghareeb E, Jalali O, Zinn Z. Infantile hemangiomas: what have we learned from propranolol? *Curr Opin Pediatr.* 2018;30(4):499–504.

Luu M, Frieden IJ. Haemangioma: clinical course, complications and management. *Br J Dermatol.* 2013;169(1):20–30.

KEY POINTS: WORRISOME HEMANGIOMAS

- **Multiple hemangiomas**: May be associated with visceral hemangiomas (most commonly liver hemangiomas)
- **Large/bulky hemangiomas**: May cause significant disfigurement of underlying structures
- **Segmental hemangiomas**: Associated with PHACE and LUMBAR syndromes
- **“Beard” hemangiomas**: May be a marker for underlying laryngeal or subglottic hemangioma that may impair respiratory function
- **Midline spinal hemangiomas**: May be a marker for underlying spinal cord abnormality
- **Head and neck hemangiomas**: Usually segmental lesions >5 cm in diameter, may be associated with other congenital anomalies
- **Vulnerable anatomic locations**: Impair vital functions or cause disfigurement (e.g., periocular, neck, lip, nasal tip)
- **Ulcerated hemangiomas**: Increased risk for infection, cause pain, and lead to scarring

168. Why is an infant with a vascular tumor and new-onset thrombocytopenia so worrisome?

This can indicate the development of the **Kasabach-Merritt syndrome** (or phenomenon), a life-threatening condition of rapidly enlarging vascular tumors and progressive coagulopathy. Platelets are sequestered within the lesion(s), forming thrombi and consuming coagulation factors. Ecchymoses may develop initially around the vascular tumor, but a disseminated coagulopathy with anemia can result. Aggressive therapy (often systemic steroids and/or vincristine and surgery) is frequently needed. Kasabach-Merritt syndrome is not caused by common infantile hemangiomas, but rather by two rare vascular tumors (kaposiform hemangioendothelioma and tufted angioma).

169. How do superficial hemangiomas differ from port wine stains?

Superficial hemangiomas are superficial, palpable, **vascular tumors** that usually involute with time. In the past, they were called “strawberry” hemangiomas. A *port wine stain,* sometimes called *nevus flammeus,* is a type of **capillary malformation** that results in flat vascular malformations composed of capillary and postcapillary venule-sized vessels that do not involute. Some superficial hemangiomas may mimic port wine stains during the first few weeks of life; observation of their growth pattern is helpful for establishing the correct diagnosis (Table 4.6).

Table 4.6 Superficial Hemangiomas Versus Port Wine Stains

SUPERFICIAL HEMANGIOMAS	PORT WINE STAINS
Palpable	Flat, macular
Common (4%-10% of children <1 year old)	Less common (0.1%-0.3%)
Often not apparent at birth (more visible at 2-12 weeks)	Present at birth
Bright red	Pale pink to blue-red (darkens with age)
Well-defined borders	Borders variable
Pathology: proliferating angioblastic endothelial cells with variable blood-filled capillaries	Pathology: dermal capillary dilation
Majority involute spontaneously by age 9 years	No involution: may worsen with darkening and hypertrophy
Rapid growth phase	Proportionate growth (as child grows)
Suggested therapy: watchful waiting; active treatment for some lesions	Suggested therapy: flash lamp pulsed-dye laser often used for facial lesions

170. What is "simple" about a nevus simplex?

Nevus simplex, also known as "stork bites" when they are on the nape of the neck and "angel's kiss" when located in the glabella and eyelids, are very common. Pink to red in color, they often fade without treatment in the first few years of life. Thus reassurance and monitoring are usually the only treatment recommended, which is a "simple" solution. Their characteristic location helps differentiate them from true facial port wine stains, which do not fade with time and may require treatment.

171. When are port wine stains associated with other anomalies?

- **Sturge-Weber syndrome** (Fig. 4.26) refers to the association of a facial port wine stain (typically affecting the skin innervated by the first branch of the trigeminal nerve), an ocular vascular anomaly linked with glaucoma, and a leptomeningeal vascular anomaly associated with seizures and developmental delay.
- **Klippel-Trenaunay syndrome** refers to the association of a limb port wine stain (usually lower extremity) with ipsilateral soft tissue and bony overgrowth and venous/lymphatic anomalies.

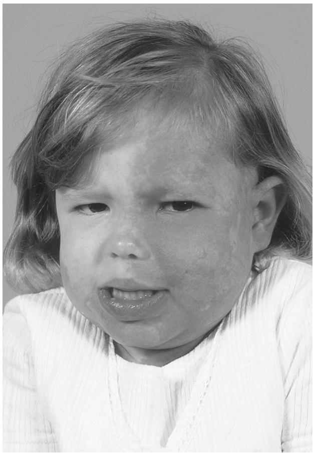

Fig. 4.26 Sturge-Weber syndrome. The bilateral port wine stain involves the V_1, V_2, and V_3 regions and the right V_3. (From Sahn EE. *Dermatology Pearls*. Philadelphia, PA: Hanley & Belfus; 1999:25.)

172. How are port wine stain–type capillary malformations treated?

Port wine stains are often pink to dark red in color during childhood. With maturity they often darken and take on their "port wine" color. Treatment of facial capillary malformations is generally recommended during infancy or early childhood when the lesions appear to be more amenable to therapy with the pulsed dye laser. The pulsed dye lasers that are used for treatment of port wine stains are designed to target oxyhemoglobin and lead to destruction of the blood vessels and subsequent lightening of the stain. Multiple treatments sometimes requiring general anesthesia or sedation are required to achieve lightening. It is important for patients and families to understand that this treatment often achieves cosmetically acceptable lightening but complete disappearance/removal of the birthmark is not yet possible with the current technologies. In some patients the stain will redarken after treatment, and touch-up treatments may be required.

VESICULOBULLOUS DISORDERS

173. What is the Nikolsky sign?

This sign demonstrates **epidermal fragility**. Gentle lateral pressure placed on apparently intact skin causes an erosion, especially near preformed vesicles. This sign is positive in several autoimmune, infectious, and inherited blistering conditions, such as bullous pemphigoid, staphylococcal scalded skin syndrome (SSSS), and EB.

174. What causes skin blistering in childhood?

- **Infectious:** bacterial (bullous impetigo, SSSS), viral (HSV, varicella)
- **Contact dermatitis**: poison ivy, phytophotodermatitis
- **Inherited disorders**: EB, bullous congenital ichthyosiform erythroderma
- **Autoimmune disorders**: linear immunoglobulin A disease, bullous pemphigoid, pemphigus vulgaris
- **Other**: erythema multiforme (EM), toxic epidermal necrolysis (TEN), thermal injury (burns)

175. How is SSSS differentiated from TEN?

Both are diffuse bullous diseases. **SSSS** commonly arises in young children <5 years old and develops after a localized staphylococcal infection with diffuse cutaneous disease caused by an exfoliative toxin. The level of blistering includes the superficial levels of the epidermis. **TEN** is believed to be a hypersensitivity reaction (often to a drug) and occurs in all age groups. The level of blistering in TEN is deep, and the entire epidermis is necrotic (Table 4.7).

Table 4.7 Differentiation Between Staphylococcal Scalded Skin Syndrome and Toxic Epidermal Necrolysis

CHARACTERISTICS	STAPHYLOCOCCAL SCALDED SKIN SYNDROME	TOXIC EPIDERMAL NECROLYSIS
Etiology	Infectious; group II staphylococci	Immunologic; usually drug related
Morbidity/mortality	Low with treatment	High
Mucous membrane involvement	Rare	Frequent
Nikolsky sign	Present	Absent
Target lesions	Absent	Often present
Level of blister	Upper epidermis (below stratum corneum)	Subepidermal
Histopathology	No epidermal necrosis or dermal inflammation	Full-thickness epidermal necrosis; prominent perivascular dermal inflammation

Adapted from Roberts LJ. Dermatologic diseases. In McMillan JA, DeAngelis CD, Feigin RD, et al., eds. *Oski's Pediatrics, Principles and Practice.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:379.

176. Why are neonates susceptible to SSSS?

The answer lies in the fact that newborns share their susceptibility to SSSS with patients in renal failure. It is the **reduced clearance of the exfoliative toxin** by the newborn's immature kidneys that contributes to their increased susceptibility to SSSS.

177. Where can the *S. aureus* be found in patients with SSSS?

S. aureus commonly colonizes the nasopharynx and the umbilicus. The source of infection may also be present in the urinary tract, a wound, conjunctiva, or blood. The bacteria are not usually present at the site of the skin lesions because they are the result of a systemic toxin-mediated effect.

178. What is the likely diagnosis for a 4-year-old child who develops a 1-week history of widespread, painful, and pruritic bullous lesions with crusting around which vesicles are arranged in a string-of-pearls appearance?

Chronic bullous dermatosis of childhood. This is the most common acquired autoimmune bullous disease of young children. It is characterized on biopsy by immunoglobulin A (IgA) and C3 deposition along the basement membrane (sometimes called *linear IgA bullous dermatosis*). Although the differential diagnosis of bullous diseases is large, the appearance of new vesicles or bullae in a "string-of-pearls" (or cluster-of-jewels) appearance around older crusted or erythematous plaques is characteristic (Fig. 4.27).

Tate C, Christian W, Newell L. Chronic bullous dermatosis of childhood and the string of pearls sign. *J Pediatr.* 2018;202:325–325.e1.

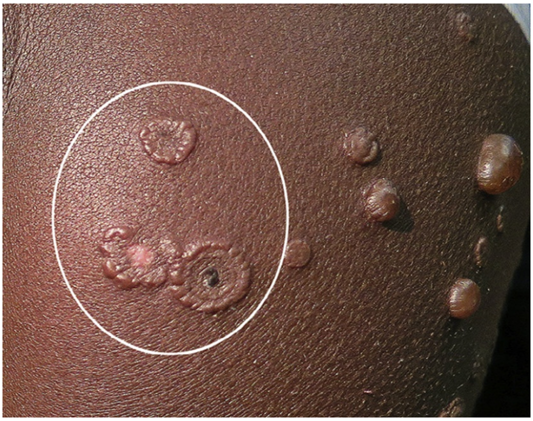

Fig. 4.27 Chronic bullous dermatitis with "string-of-pearls" vesicles around older lesions. (From Tate C, Christian W, Newell L. Chronic bullous dermatitis of childhood and the string of pearls sign. *J Pediatr.* 2018;202:325.)

179. What are the subtypes of EB?

EB is a heterogeneous group of inherited disorders characterized by the formation of blisters and erosions at sites of friction or trauma. There are three subtypes of EB that are categorized based on the region of the dermal-epidermal junction (DEJ) affected: **simplex**, **junctional**, and **dystrophic**. The extent of blistering and the degree of scarring roughly correlate with the level of blister formation in the epidermis or dermis. A fourth subtype of EB has been added, **Kindler syndrome**, which affects multiple layers of the DEJ.

Dystrophic Epidermolysis Bullosa Research Association of America. www.debra.org. Accessed January 18, 2020.

180. Should EB blisters be "popped"?

Yes. Because patients with EB have a genetic abnormality of the proteins that hold their epidermis and dermis together, the pressure from simple accumulation of fluid within an intact blister can cause the blister to expand. The blister should be drained by a sterile needle or lancet after a gentle sterile alcohol prep of the site. The blister roof should be left intact.

181. Which disorder is associated with "target lesions"?

EM. This is typically an acute, self-limited, but sometimes recurring skin condition (*EM minor*) believed to be a T-cell–mediated immune reaction most commonly to certain infections (e.g., HSV, streptococcal, Epstein-Barr virus [EBV]) but also to a variety of other triggers, particularly medications (e.g., sulfa drugs, penicillins, anticonvulsants). In *EM major,* erosions or bullae of the oral, genital, or ocular mucosa occur. Most mild cases resolve over 1 to 2 weeks. The characteristic target lesions occur as dusky, red papules that evolve into depressed, localized, damaged epithelium with spreading annular edema (pale) and inflammation on the periphery (erythema) (Fig. 4.28).

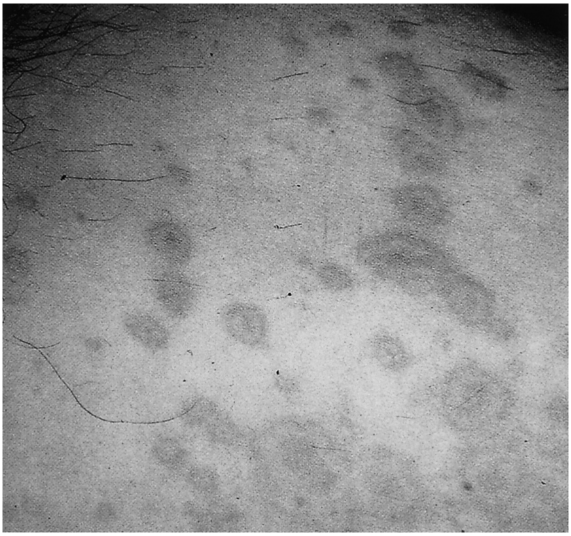

Fig. 4.28 Erythema multiforme with typical target lesions. (From Goldbloom RB. *Pediatric Clinical Skills*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011: color plate 19–11.)

182. Is EM part of a continuum with Stevens-Johnson syndrome (SJS) and TEN?

This is an area of controversy. Traditionally, these had been viewed as related disorders because they had some shared clinical and histologic features. However, the majority of EM cases are associated with infections, while SJS/TEN occurrences are believed to be drug related in >90% of cases. There are also distinctions according to anamnesis (history), morphology, involved sites, extension of lesions, and pathogenic mechanisms. Current opinion favors these as distinct conditions, with SJS/TEN not being the end-stage result of some cases of EM.

Iwai S, Sueki H, Watanabe H, et al. Distinguishing between erythema multiforme major and Stevens-Johnson syndrome/toxic epidermal necrolysis immunopathologically. *J Dermatol.* 2012;39(9):781–786.

183. What distinguishes SJS from TEN?

Both are severe mucocutaneous disorders that are characterized by extensive necrosis and epidermal detachment. They are believed to be a continuum, usually triggered by medications, and are distinguished primarily based on the percentage of body surface that is involved. SJS is the less severe of the two, defined as <10% body surface involvement. TEN encompasses >30% of body area. Between 10% and 30% indicates a classification overlap.

184. What medications are most commonly associated with SJS and TEN in children?

Sulfonamides and **anticonvulsants**, especially phenobarbital, carbamazepine, and lamotrigine. Less common causes are penicillins and nonsteroidal anti-inflammatory drugs (NSAIDs). Very rarely, acetaminophen may be involved.

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Arch Dis Child.* 2013;98(12):998–1003.

185. What are treatments for SJS or TEN?

This is a continuing area of controversy; studies are inconclusive. In SJS, *systemic steroids* may be considered early during the course if multiple mucosal surfaces are involved but skin denudation is limited. If initiated, clinical response (or lack thereof) should be carefully followed, and steroids should be discontinued if the condition is worsening. Steroids have been reported to be associated with an increased mortality rate among patients with TEN. *Intravenous immune globulin* should be considered for rapidly progressive disease. Caution should be used, especially in patients with poor renal function, hypercoagulable states, or IgA deficiency. *Cyclosporine* and *tumor necrosis factor alpha* (*TNF alpha) inhibitors* have also been used. Supportive care, including skin care, nutritional support, ophthalmologic care, and the treatment of secondary bacterial infections, is vital to maximize outcomes.

Schneider JA, Cohen PR. Stevens-Johnson syndrome and toxic epidermal necrolysis: a concise review with a comprehensive summary of therapeutic interventions emphasizing supportive measures. *Adv Ther.* 2017;34(6):1235–1244.

Finkelstein Y, Soon GS, Acuna P, et al. Recurrence and outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Pediatrics.* 2011;128(4):723–728.

186. What is MIRM?

MIRM is the acronym for *Mycoplasma-induced rash and mucositis,* which is an extrapulmonary condition of rash and mucosal erosions that occurs in the setting of an *Mycoplasma pneumoniae* infection. The dermatologic findings can mimic those of drug-induced SJS.

Canavan TN, Mathes EF, Frieden I, Shinkai K. Mycoplasma pneumoniae-induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: a systematic review. *J Am Acad Dermatol.* 2015;72(2):239–245.

187. In addition to hand–foot–mouth, which other body site is often affected in children with Coxsackie virus infections?

Coxsackie viral infections often also cause skin lesions on the **buttocks**, prompting some clinicians to call the condition “hand–foot–mouth–butt (or ‘tuchus’) syndrome.”

Mohr MR, Sholtzow M, Bevan HE, et al. Exploring the differential diagnosis of hemorrhagic vesicopustules in a newborn. *Pediatrics.* 2011;127(1):e226–e230.

188. *Peau d’orange* appearance to the skin is a clue to which blistering disorder?

Diffuse cutaneous mastocytosis may present with blisters and erosions. A *peau d’orange* (skin of an orange) appearance may be seen at sites of edema.

Hosking AM, Makdisi J, Ortenzio F, et al. Diffuse cutaneous mastocytosis: case report and literature review. *Pediatr Dermatol.* 2018;35(6): e348–e352.

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EMERGENCY MEDICINE

Joan S. Bregstein, MD, Elizabeth Prabhu, MD and Meridith Sonnett, MD

CHAPTER 5

BIOTERRORISM

1. Why are children more vulnerable to biologic agents than adults?

- **Anatomic and physiologic differences:** Thinner dermis, increased surface area–to–volume ratio, smaller relative blood volume, higher minute ventilation
- **Developmental considerations:** Inability to flee dangerous situations, possible increased risk for posttraumatic stress disorder (PTSD)
- **Some vaccines not licensed for children:** Anthrax (18 to 65 years), plague (18 to 61 years)
- **Vaccines more dangerous in children:** Smallpox, yellow fever
- **Antibiotics less familiar to pediatricians:** Tetracyclines, fluoroquinolones

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Zhao X, Dughly O, Simpson J. Decontamination of the pediatric patient. *Curr Opin Pediatr.* 2016;28(3):305–309.
Cieslak TJ, Henretig FM. Bioterrorism. *Pediatr Ann.* 2003;32(3):145–165.

2. What are the three routes of transmission of anthrax?

- **Inhalation:** Most feared; can lead to multiorgan hemorrhagic necrosis
- **Cutaneous:** Inoculated through a wound, causing a black, painless ulcer
- **Ingestion:** May cause gastrointestinal (GI) or upper respiratory symptoms

Bacillus anthracis, which is a spore-forming gram-positive rod, can survive for extended periods before entering the body, where it will germinate and proliferate (Fig. 5.1).

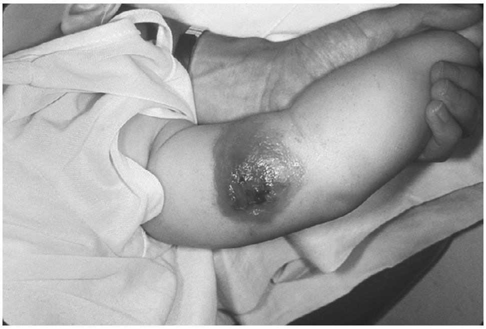

Fig. 5.1 Cutaneous anthrax in a child. (From Schachner LA, Hansen RC, eds. *Pediatric Dermatology*. 3rd ed. Edinburgh, Scotland: Mosby; 2003:1033.)

3. How are the lesions of smallpox distinguished from varicella (chickenpox)?

- *Smallpox* lesions predominate on the face and extremities (centrifugal), whereas *varicella* lesions are typically heaviest on the trunk (centripetal).
- Rash of *smallpox* progresses in similar stages (macules, papules, vesicles, crusting), whereas *varicella* is seen with multiple crops in differing stages.
- *Smallpox* rash develops more slowly than *varicella* rash.

4. How can the presenting symptoms of bubonic plague be differentiated from those of plague resulting from bioterrorism?

Bubonic plague—of "black death" fame—resulted from the bite of fleas, which led to a large, tender, regional adenopathy (the "bubo") with subsequent hematogenous dissemination, multiorgan involvement, and septicemia. In bioterrorism, the organism *Yersinia pestis* could be aerosolized, and inhalation would result in presentations more typical of pneumonic plague, with fever, chills, tachypnea, cough, and bloody sputum; lymphadenitis would likely be a later finding.

Kwon EH, Reisler RB, Cardile AP, et al. Distinguishing respiratory features of category A/B potential bioterrorism agents from community-acquired pneumonia. *Health Secur.* 2018;16(4):224–238.
Dennis DT, Chow CC. Plague. *Pediatr Infect Dis J.* 2004;23(1):69–71.

5. Why should families living near nuclear power plants keep potassium iodide (KI) in their medicine cabinets?

Multiple organizations recommend that families living within 10 miles of a nuclear power plant (or 50 miles in densely populated areas, where evacuations may be more difficult) have KI on hand in the event of a nuclear radiation catastrophe. KI will inhibit the uptake of any released radioactive iodine (^{131}I) into the thyroid gland. Children are more susceptible than adults to the subsequent development of thyroid cancer if exposed. If KI is administered within 1 hour, 90% of ^{131}I is blocked, but after 12 hours, there is little effect. Of note, beyond the 10-mile radius, the major risk for ^{131}I exposure is from ingestion of contaminated foodstuffs.

Leung AM, Bauer AJ, Benvenga S, et al. American Thyroid Association scientific statement on use of potassium iodide ingestion in a nuclear emergency. *Thyroid.* 2017;27(7):865–877.

Committee on Environmental Health, American Academy of Pediatrics. Radiation disasters and children. *Pediatrics.* 2003; 111(6 Pt 1):1455–1466.

6. Why are children particularly vulnerable to terrorism in the form of explosive and blast attacks?

- Smaller mass results in greater force per unit of body surface from energy released by explosion.
- Children are more susceptible to fractures as a result of incompletely calcified growth plates.
- The chest wall has greater pliability in children, resulting in greater chance of cardiac and pulmonary injury from blast explosives.

Bull A, Mayhew E, Reavley P, et al. Paediatric blast injuries: challenges and priorities, *Lancet Child Adolesc Health.* 2018;2(5):310–311.

Garth RJN. Blast injury of the ear: an overview and guide to management. *Injury.* 1995;26(6):363–366.

7. What categories of agents should be considered in the event of a chemical weapons attack?

- **Nerve:** Nerve agents are similar to organophosphate insecticides and include cholinesterase inhibitors, such as sarin, soman, and VX. Nerve agents inhibit the action of acetylcholinesterase at cholinergic neural synapses, where acetylcholine then accumulates. These agents are generally colorless, odorless, tasteless, and nonirritating to the skin. Nerve agent vapors are denser than air and tend to accumulate in low-lying areas, putting children at a higher risk than adults for exposure. The agents used in terrorist attacks are inhaled and absorbed through skin and mucous membranes.
- **Asphyxiants:** Asphyxiants are toxic compounds that inhibit cytochrome oxidase, causing cellular anoxia and lactic acidosis (high anion gap). Hydrogen cyanide, the most commonly known toxicant in this class, is a colorless liquid or gas that smells like bitter almonds. Exposure to hydrogen cyanide produces rapid onset of tachypnea, tachycardia, and flushed skin, followed by nausea, vomiting, confusion, weakness, trembling, seizures, and death.
- **Choking and pulmonary agents:** Choking agents include chlorine and phosgene. When inhaled, these agents produce massive mucosal irritation and edema, as well as significant damage to lung parenchyma.
- **Blistering and vesicant agents:** Blistering agents include sulfur mustard and lewisite. Sulfur mustard is an alkylating agent that is highly toxic to rapidly reproducing and poorly differentiated cells; skin, pulmonary parenchyma, and bone marrow are frequently damaged. Lewisite is an arsenical compound that affects skin and eyes immediately on exposure.

8. What should be the practitioner's initial management when a chemical weapons event occurs?

The single most important first step for treating all chemical exposures is the **initial decontamination strategy**. Immediate removal of patient clothing can eliminate about 90% of contaminants.

CHILD ABUSE: PHYSICAL AND SEXUAL

9. What are important historical indicators of possible child abuse?

- Multiple previous hospital visits for injuries
- History of untreated injuries
- Cause of trauma not known or inappropriate for age or activity
- Delay in seeking medical attention
- History incompatible with injury
- Parents unconcerned about injury or more concerned about unrelated minor problem (e.g., cold, headache)
- History of abused siblings
- Changing or inconsistent stories to explain injury
- History of child abuse in either parent as children
- History of prematurity in child

Berkowitz CD. Physical abuse of children. *N Engl J Med.* 2017;376(17):1659–1666.

Glick JC, Lorand MA, Bilka KR. Physical abuse of children. *Pediatr Rev.* 2016;37(4):146–156.

Kottmeier P. The battered child. *Pediatr Ann.* 1987;16(4):343–351.

10. What is the most common cause of severe closed head trauma in infants younger than 1 year?

Abusive head trauma. This is the terminology adopted by the American Academy of Pediatrics (AAP) to replace the term *shaken baby syndrome*. It describes inflicted injury in infants and young children that results either from an impact to the head or violent shaking of the head, or a combination of both mechanisms. The term *shaken baby syndrome* was changed because it implied a knowledge on the part of the treating clinician of the mechanism of injury that was most often not known. Abusive head trauma is most common in infants <1 year of age and, compared with accidental head injury, has a much greater mortality rate. Male infants and those from lower socioeconomic groups tend to be at highest risk. Abusive head trauma manifests as subdural hematomas, subarachnoid hemorrhages, and cerebral infarcts. The diagnosis is suggested by the lack of a corroborating mechanism of injury in the face of a symptomatic child or, rarely, a confession by the perpetrator. In many cases, physical examination reveals retinal hemorrhages (Fig. 5.2); other signs of trauma are usually lacking. Diagnosis is confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). If a lumbar puncture is performed, the fluid may be bloody or xanthochromic. The prognosis is grim for an infant who is in a coma from this abuse: 50% die, and nearly half of the survivors have significant neurologic sequelae.

Christian CW, Levin AV, Council on Child Abuse and Neglect. The eye examination in the evaluation of child abuse. *Pediatrics.* 2018;142(2):e20181411.

Narang S, Clarke J. Abusive head trauma: past, present and future. *J Child Neurol.* 2014;29(12):1747–1756.

Christian CW, Block R, Committee on Child Abuse and Neglect. Abusive head trauma in infants and children. *Pediatrics.* 2009;123(5):1409–1411.

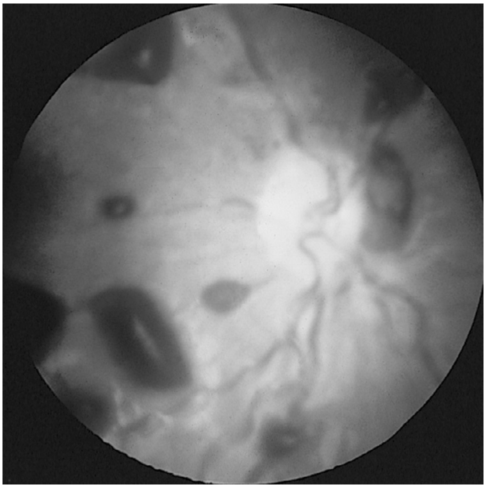

Fig. 5.2 Retinal hemorrhages of victim of abusive head trauma. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis*. 4th ed. St. Louis, MO: Mosby; 2002:181.)

11. Why is the diagnosis of abusive head trauma often overlooked?

When an infant is unconscious with respiratory distress, apnea, and/or seizures, the diagnosis of abusive head trauma should be considered. However, depending on the degree of impact or shaking and the degree of resulting damage, the symptoms can be mild and nonspecific and may mimic symptoms of a viral illness, feeding disorder or dysfunction, or even colic. Victims may have a history of poor feeding, vomiting, lethargy, and/or irritability that may have gone on for days or weeks. Early identification of abusive injuries is critical because of the risk for increased mortality with each recurrent abusive event.

Pierce MC, Kaczor K, Acker D, et al. History, injury and psychosocial risk factor commonalities among cases of fatal and near-fatal physical child abuse. *Child Abuse Negl.* 2017;69:263–277.

12. What diagnostic tests should be considered if abusive head trauma is suspected?

- **Head CT:** Good for demonstrating subarachnoid and large extra-axial hemorrhages and mass effect; may be falsely negative, especially early in the presentation

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[Ahmed Manfy] on TELEGRAM

- **MRI:** Good for diagnosing subdural hemorrhages and intraparenchymal lesions; may miss subarachnoid blood and fractures
- **Spinal tap:** May yield bloody cerebrospinal fluid
- **Skeletal survey:** May be normal or may reveal acute or healed rib or other fractures, which are suggestive of abuse
- **Complete blood count:** May be normal or may show mild to moderate anemia
- **Prothrombin time and partial thromboplastin time:** May show mild to moderate abnormalities or reveal frank disseminated intravascular coagulation (DIC)
- **Amylase:** May show an increase, signifying possible pancreatic damage
- **Liver function tests:** Abnormalities may signify occult liver injury

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Choudhary AK, Servaes S, Slovis TL, et al. Consensus statement on abusive head trauma in infants and young children. *Pediatr Radiol.* 2018;48(8):1048–1065.

13. What physical examination findings are indicators of possible child abuse?

- Burns, especially cigarette or immersion burns, on the buttocks or perineum or burns in a stocking-and-glove distribution
- Genital trauma or sexually transmitted infection (STI) in a prepubertal child
- Signs of excessive corporal punishment (welts, belt or cord marks, bites)
- Frenulum lacerations in young infants or tongue bruising (associated with forced feeding)
- Multiple bruises in various stages of resolution
- Bruises in a premobile infant
- Neurologic injury associated with retinal or scleral hemorrhages
- Fractures suggestive of abuse (e.g., skull fractures in infants, metaphyseal fractures, posterior rib fractures, fractures in premobile infants, scapular fractures in infants beyond the immediate newborn period)

Glick JC, Lorand MA, Bilka KR. Physical abuse of children. *Pediatr Rev.* 2016;37(4):146–156.

Kottmeier P. The battered child. *Pediatr Ann.* 1987;16(4):343–351.

14. If physical abuse is suspected, are physicians mandated to photograph physical findings?

No. A good drawing of the physical findings is sufficient. However, if photographs are taken, a card with the patient's name and date of birth and the photographer's name and signature must be included in the photograph so that the patient can be clearly identified. In addition, the body part that is being photographed must be clearly identifiable. If abuse is suspected, it is not necessary to obtain parental consent to take photographs.

15. If retinal hemorrhages are noted in a child with seizures, how likely are the seizures to have caused the hemorrhages?

In theory, any seizure may cause retinal hemorrhages through a sudden rise in retinal venous pressure in conjunction with increased central venous and intrathoracic pressure. However, a prospective study of children with seizures who had ophthalmologic evaluation found no evidence of an association of seizures and retinal hemorrhages. Combining their data with some previous studies, the authors determined a prevalence of retinal hemorrhages with a seizure of only about 3 per 10,000—an extremely small likelihood. If retinal hemorrhages are found in a child with seizures, the possibility of nonaccidental injury must be explored.

Hansen JB, Killough EF, Moffatt ME, Knapp JF. Retinal hemorrhages: abusive head trauma or not? *Pediatr Emerg Care.* 2018; 34(9):665–670.

Curcoy AI, Trenchs V, Morales M, et al. Do retinal haemorrhages occur in infants with convulsions? *Arch Dis Child.* 2009;94(11):873–875.

16. In a suspected victim of child abuse, how common are retinal hemorrhages if neuroimaging reveals no evidence of traumatic brain injury?

Very rare. Research has demonstrated that in the absence of positive neuroimaging, it is unlikely that an ophthalmologic eye examination will reveal clinically significant retinal hemorrhages in suspected child abuse.

Greiner MV, Berger RP, Thackeray JD, et al. Dedicated retinal examination in children evaluated for physical abuse without radiographically identified traumatic brain injury. *J Pediatr.* 2013;163(2):527–531.

Thackeray JD, Scribano PV, Lindberg DM. Yield of retinal examination in suspected physical abuse with normal neuroimaging. *Pediatrics.* 2010;125(5):e1066–e1071.

17. Which conditions with ecchymoses (bruising) can be mistaken for child abuse?

- **Mongolian spots (dermal melanocytosis)** are commonly mistaken for bruises, especially when they occur elsewhere than the classic lumbosacral area; unlike bruises, they fade very slowly with time (Fig. 5.3).

- **Coagulation disorders** including hemophilia or von Willebrand disease. In 20% of cases of hemophilia, there is no family history of disease; bruising may be noted in unusual places in response to minor trauma.
- **Folk medicine** such as the Southeast Asian practices of spoon rubbing (quat sha) or coin rubbing (cao gio) can produce ecchymoses; the practice of cupping (the inversion of a heated cup on the back) produces circular ecchymoses.
- **Moxibustion** is the Southeast Asian practice of burning an herbal substance on the child's abdomen to cure disease.
- **Clothing** dyes, especially from jeans, sometimes mimic bruising; they are easily removed with topical alcohol.
- **Vasculitis**, particularly Henoch-Schönlein purpura with a purpuric rash most commonly on the buttocks and lower extremities, or idiopathic thrombocytopenic purpura (ITP) may be mistaken for signs of child abuse.
- **Vitamin K deficiency**

Ward MGK, Ornstein A, Niec A, et al. The medical assessment of bruising in suspected child maltreatment cases: a clinical perspective. *Paediatr Child Health.* 2013;18(8):433–437.

Kaczor K, Pierce MC, Makoroff K, Corey TS. Bruising and physical child abuse. *Clin Pediatr Emerg Med.* 2006;7:153–160.

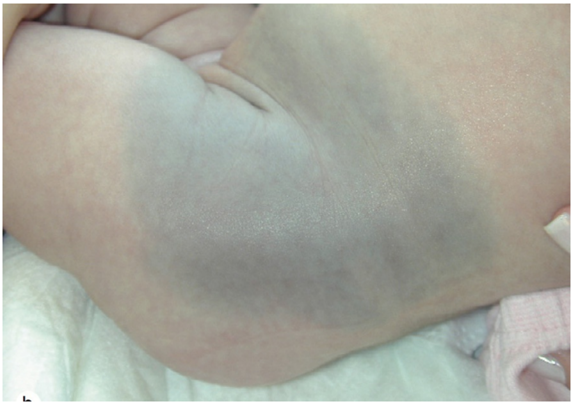

Fig. 5.3 Dermal melanocytosis (Mongolian spot) on the left hip and abdomen of a light-pigmented infant. (From Cohen BA. *Pediatric Dermatology.* 4th ed. Philadelphia, PA: Elsevier; 2013:155.)

18. How do bruising patterns differ in abused children compared with nonabused children?

Derived at Kosair Children's Hospital in Louisville, a simple mnemonic "**TEN 4**," which assesses body region and age, can be useful in identifying bruises that are of concern for abuse.

TEN stands for **To**rso, **E**ar, and **N**eck and **4** refers to ages ($<$4 months or $\leq$4 years). In the context of no confirmed accident in a public setting that would account for bruising, any bruising in an infant $<$4 months or bruising in the TEN region of a child $\leq$4 years was highly sensitive and specific for abusive trauma. Another study of 203 children $<$3 years of age found bruises were quite uncommon in children not yet walking with support and cautioned that "those who don't cruise rarely bruise." In general, the head and face are the most common sites of bruising in abused children. Clustering of bruises may represent defensive injuries, and abusive bruises may carry an imprint of a hand or the looped mark of an extension cord.

Pierce MC, Kaczor K, Aldridge S, et al. Bruising characteristics discriminating physical child abuse from accidental trauma. *Pediatrics.* 2010;125(1):67–74.

Sugar NF, Taylor JA, Feldman KW. Bruises in infants and toddlers: those who don't cruise rarely bruise. *Arch Pediatr Adolesc Med.* 1999;153(4):399–403.

19. What screening laboratory tests should be obtained if you suspect nonaccidental abdominal injury?

It is important to remember that pediatric victims of nonaccidental trauma can be symptomatic with signs of hemorrhage or peritonitis, or they may not exhibit overt findings. If you are suspicious of abdominal injury, the workup should include:

- Liver and pancreatic enzyme levels
- Urinalysis
- Contrast-enhancing CT when screening laboratory tests suggest abdominal injury; in all cases of symptomatic injury; and most cases when the physical examination is unreliable because of the patient's age, presence of distracting injuries, or presence of accompanying head injury.

Christian CW. The evaluation of suspected child physical abuse. *Pediatrics.* 2015;135(5):e1337–e1354.

20. How are fractures dated radiographically in children?

After a fracture, the following will be seen:

- **1 to 7 days:** Soft tissue swelling; fat and fascial planes blurred; sharp fracture line
- **7 to 14 days:** Periosteal new bone formation as soft callus forms; blurring of fracture line; occurs earlier for infants, later for older children
- **14 to 21 days:** More clearly defined (i.e., hard) callus forming as periosteal bone converts to lamellar bone
- **21 to 42 days:** Peak of hard callus formation
- **$\geq$60 days:** Remodeling of bone begins with reshaping of the deformity (up to 1 to 2 years)

If the timing of an injury does not correlate with the dating of a fracture or if fractures are at multiple stages of healing are present, child abuse should be suspected.

21. What fractures are suggestive of child abuse?

All fractures can be the result of child abuse, and a careful history will guide the clinician in the degree of suspicion indicated in each case. In infants and toddlers, physical abuse is the cause of up to 20% of fractures. This is an age group in which suspicion should be high. Some fractures have been shown to have a high specificity for abuse, and these are **rib fractures in infants**, particularly posteromedially; classic **metaphyseal lesions of long bones**; and **fractures of the scapula, spinous process,** and **sternum**. Metaphyseal fractures (Fig. 5.4) require shearing forces not usually produced in accidental trauma, with an increased likelihood of mechanisms that involve shaking with limbs flailing, twisting, and jerking. The presence of multiple fractures, fractures of

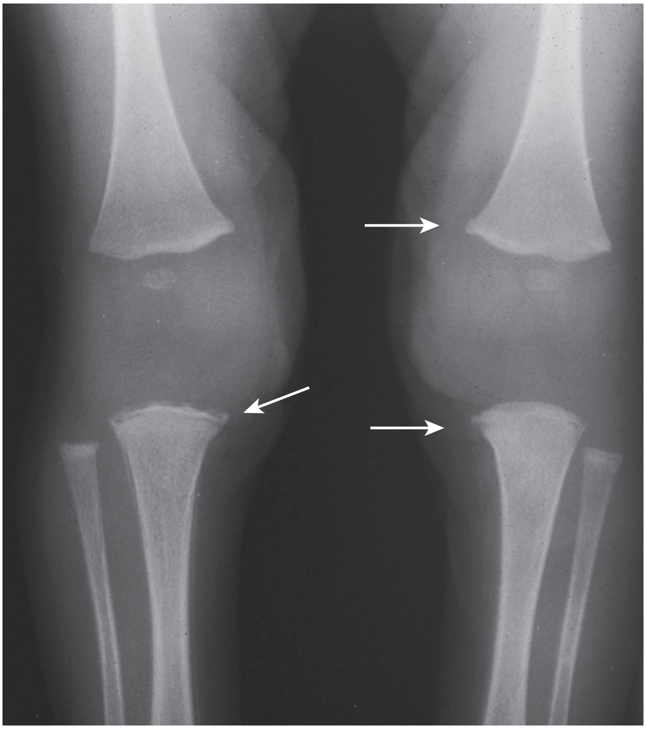

Fig. 5.4 Radiograph of classic metaphyseal *(arrows)* lesions. (From Jenny C, ed. *Child Abuse and Neglect.* Philadelphia, PA: Elsevier Saunders; 2011:285.)

different ages and/or stages of healing, and complex skull fractures also have a good degree of specificity for abuse.

Flaherty EG, Perez-Rossello JM. Evaluating children with fractures for child physical abuse. *Pediatrics.* 2014;133(2):e477–e489.
Pierce MC, Bertocci G. Fractures resulting from inflicted trauma: assessing injury and history compatibility. *Clin Pediatr Emerg Med.* 2006;7:143–148.

22. How certain can a clinician be in attributing a femur fracture in a nonambulatory child to nonaccidental trauma?

Femur fractures in the nonambulatory child are most often the result of nonaccidental trauma. However, there are exceptions to this “rule.” Certain femur fractures in young children may be accidental:

- A short fall to the knee may produce a torus or impacted transverse fracture of the distal femoral metaphysis.
- Children playing in a stationary activity center, like an Exersaucer, may sustain an oblique distal femur metaphyseal fracture.
- Falls down a stairway in a nonambulatory child can sometimes cause one leg to become twisted underneath the child, resulting in a spiral femoral fracture.

Wood JN, Fakeye O, Mondestin V, et al. Prevalence of abuse among young children with femur fractures: a systematic review. *BMC Pediatr.* 2014;14:169.
Haney SB, Boos SC, Kutz TJ, et al. Transverse fracture of the distal femoral metadiaphysis: a plausible accidental mechanism. *Pediatr Emerg Care.* 2009;25(12):841–844.
Pierce MC, Bertocci GE, Janosky JE, et al. Femur fractures resulting from stair falls among children: an injury plausibility model. *Pediatrics.* 2005;115(6):1712–1722.

23. What is the purpose of the skeletal survey?

Skeletal injuries, particularly multiple healed lesions, are strong indicators of a pattern of abuse. The *skeletal survey* is a radiologic evaluation of multiple bones in the body to:

- Reveal fractures of additional bones (new or healing) other than the fractured bones already known to the clinician
- Reveal fractures (new or healing) in a child suspected of abuse manifesting in ways other than fractures.

Paine CW, Wood JN. Skeletal surveys in young, injured children: a systematic review. *Child Abuse Negl.* 2018;76:237–249.

24. What constitutes a skeletal survey?

The skeletal survey is a multiple-imaging series that includes x-ray views of the following:

- **Appendicular skeleton:** Humeri, forearms, hands, femurs, lower legs, and feet
- **Axial skeleton:** Thorax, pelvis, entire spine and head CT

The series can include anywhere between 19 and 30 x-rays. “Body grams” (studies that encompass the entire child in one or two exposures) are not thought to be of sufficient sensitivity to be useful.

Borg K, Hodes D. Guidelines for skeletal survey in young children with fractures. *Arch Dis Child Educ Pract Ed.* 2015; 100(5):10.1136.
American Academy of Pediatrics, Section on Radiology. Diagnostic imaging of child abuse. *Pediatrics.* 2009;123(5):1430–1431.

25. Up to what age should a skeletal survey be ordered?

If physical abuse is suspected, the AAP recommends a mandatory study in children up to the age of 2 years. The yield diminishes after that age and is of little value after the age of 5 years.

American Academy of Pediatrics, Section on Radiology. Diagnostic imaging of child abuse. *Pediatrics.* 2009;123(5):1432.

26. What is the value of a follow-up skeletal survey?

Both the AAP and the American College of Radiology recommend follow-up skeletal surveys about 2 to 3 weeks after the initial study if the first was abnormal or equivocal or when abuse is suspected on clinical grounds despite a normal first study. The follow-up skeletal survey can demonstrate a previously missed occult fracture by the presence of new callus formation. The yield can be substantial, with studies demonstrating new findings ranging from 14% to 61%. Because of the additional radiation, research is also addressing the applicability of more limited views on the follow-up study.

Hansen KK, Keeshin BR, Flaherty E, et al. Sensitivity of the limited view follow-up skeletal survey. *Pediatrics.* 2014;134(2):242–248.

27. Can an initial skeletal survey be limited with fewer x-rays to reduce radiation exposure?

Not yet, but there is considerable debate. Views of the spine and pelvis have the lowest yield in revealing fractures, and they require the largest amounts of radiation. Some researchers believe these views could be eliminated without missing cases of abuse. They advocate for a stepwise approach to imaging that would protocolize a “core” skeletal survey, without lateral spine and pelvis, but would encourage inclusion of these views if clinically indicated. The complicating factor is that fractures of the spine and pelvis are highly specific for abuse when they are found. Some researchers believe it would be dangerous to eliminate these views from the initial skeletal survey.

Slovis TL, Strouse PJ, Strauss KJ. Radiation exposure in imaging of suspected child abuse: benefits versus risk. *J Pediatr.* 2015;167(5):963–968.

Lindberg DM, Harper NS, Laskey AL, et al. Prevalence of abusive fractures of the hands, feet, spine, or pelvis on skeletal survey. *Pediatr Emerg Care.* 2013;29(1):26–29.

Karmazyn B, Lewis ME, Jennings SG, et al. The prevalence of uncommon fractures on skeletal surveys performed to evaluate for suspected abuse in 930 children: should practice guidelines change? *Am J Radiol.* 2011;197(1):W159–W163.

28. In addition to child abuse, what conditions must you consider as a cause of multiple unexplained long bone fractures in a young child?

- **Osteogenesis imperfecta** (OI) is a rare congenital disorder that presents with bone fragility. In addition to frequent fractures, patients with this disorder often present with the following:
  - Blue sclera
  - Ligamentous laxity
  - Osteopenia
  - Wormian skull bones (additional isolated sutural lines on skull x-ray)
  - Dentinogenesis imperfecta
  - Family history of OI (although not always because new cases can result from de novo mutations)
  - Hearing loss
- **Vitamin D deficiency–associated rickets**
- **Scurvy**
- **Copper deficiency**

29. When are burn injuries suspicious for child abuse?

Burn injuries account for about 5% of cases of physical abuse. As with other injuries, the description of the incident causing the burn should be consistent with the child’s development and the extent and degree of the burn observed. The following types are suspicious for abuse:

- **Immersion burns:** Sharply demarcated lines on the hands and feet (stocking-and-glove distribution), buttocks, and perineum, with a uniform depth of burn; the immersion of a child in a hot bath is a classic example
- **Geographic burns:** Burns, usually of second or third degree, in a distinct pattern, such as circular cigarette burns or steam iron burns
- **Splash burns:** Pattern with droplet marks projecting away from the most involved area; splash marks on the back of the body usually require another person and may or may not be accidental

30. How do you recognize fabricated child abuse?

This form of child abuse, previously called Munchausen syndrome by proxy, now goes by various names, including pediatric condition falsification, abuse by pediatric condition falsification, caregiver-fabricated illness in a child, medical child abuse, or factitious disorder imposed on another. Adult caregivers (most commonly the patient’s mother) inflict illness on a child or falsify symptoms to obtain medical care for a child. Features include the following:

- Recurrent episodes of a confusing medical picture
- Multiple diagnostic evaluations at different medical centers (“doctor shopping”)
- Unsupportive marital relationship, often with maternal isolation
- Compliant, cooperative, and overinvolved mother
- Higher level of parental medical knowledge
- Parental history of extensive medical treatment or illness
- Conditions resolve with surveillance of the child in the hospital
- Findings correlate with the presence of the parent

Yates G, Bass C. The perpetrators of medical child abuse (Munchausen syndrome by proxy): a systematic review of 796 cases. *Child Abuse Neg.* 2017;72:45–53.

Stirling J. Beyond Munchausen syndrome by proxy: identification and treatment of child abuse in a medical setting. *Pediatrics.* 2007;119(5):1026–1030.

31. How often is sexual abuse committed by an individual known previously by the child or adolescent?

Between 75% and 80% of the time. Relatives are the perpetrators in about one-third of cases.

32. In the case of suspected prepubertal sexual abuse, how critical is it to perform the physical examination immediately on presentation of the child to a medical facility?

If no exchange of bodily fluids has occurred and the child is not presenting with a medical emergency, such as vaginal bleeding, it is not necessary to perform a medical examination immediately in the office or emergency department (ED) setting. In fact, it is preferential to refer the child to a setting staffed by medical personnel familiar with the sexual abuse examination, such as a pediatric ED or a child advocacy center. If exchange of bodily fluids has occurred, then the timing of the examination is more critical. Guidelines vary from state to state, with recommendations that forensic evidence be collected from 24 hours to 96 hours after an assault.

33. After the documentation of history and a careful physical examination, what evidence should be collected in cases of suspected sexual abuse in a *prepubertal* female?

Because STIs are not common in prepubertal children evaluated for abuse, culturing all sites (vaginal, rectal, and oral) for all organisms is not recommended if the child is not symptomatic. Each case should be treated individually. However, here are some considerations:

- Whether the child was penetrated, either vaginally or anally
- Whether the abuser was a stranger
- Whether the abuser is known to have an STI or be at risk
- Whether the child has a sibling or other relative in the household with an STI
- Whether the child has signs or symptoms of an STI
- Whether the child has already been diagnosed with a previous STI

If the decision is made to collect specimens from a prepubertal child, the AAP recommends the use of a nucleic acid amplification test (NAAT) for detection of infection with *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Culture-based tests for these organisms are highly insensitive. However, it should be noted that the Food and Drug Administration (FDA) has not approved the use of the NAAT for cultures of the rectum and throat in pediatric patients.

Jenny C, Crawford-Jakubiak JE. The evaluation of children in the primary care setting when sexual abuse is suspected. *Pediatrics.* 2013;132(2):e558–e567.

34. After the documentation of history and a careful physical examination, what evidence should be collected in cases of suspected sexual abuse in a *postpubertal* female?

- Pregnancy test, if postmenarchal
- Evidence of sexual contact, including two to three swabbed specimens from each area of assault for the following substances: sperm (motile and nonmotile), acid phosphatase (secreted by the prostate; component of seminal plasma), P_{30} (prostate glycoprotein present in seminal fluid), blood group antigens
- NAAT for STIs from all three sites
- Evidence to document perpetrator: foreign material on clothing, suspected nonpatient hairs; DNA testing (controversial)

Jenny C, Crawford-Jakubiak JE. The evaluation of children in the primary care setting when sexual abuse is suspected. *Pediatrics.* 2013;132(2):e558–e567.

35. After the initial ED evaluation for sexual assault, what kind of follow-up care should the ED physician offer?

- Human immunodeficiency virus (HIV) follow-up counseling with infectious disease or HIV specialist in 3 to 5 days
- Follow-up gynecologic examination at 1 to 2 weeks
- Repeat serologic tests for syphilis and HIV in 6 weeks, 3 months, and 6 months
- Psychiatric counseling

36. If a child who is not sexually active is diagnosed with an infection caused by an STI-associated organism, how likely is sexual abuse the reason for acquisition?

See Table 5.1.

Table 5.1 Likelihood of Sexual Abuse According to Organism

ORGANISM	LIKELIHOOD OF SEXUAL ABUSE
Neisseria gonorrhoeae	Diagnostic
Treponema pallidum (syphilis)	Diagnostic
Chlamydia trachomatis	Diagnostic
Human immunodeficiency virus	Diagnostic
Trichomonas vaginalis	Highly suspicious

Continued on following page

Table 5.1 Likelihood of Sexual Abuse According to Organism (*Continued*)

ORGANISM	LIKELIHOOD OF SEXUAL ABUSE
Genital herpes	Highly suspicious (HSV-2 especially)
Condyloma acuminate (anogenital warts)	Suspicious
Bacterial vaginosis	Inconclusive

Adapted from American Academy of Pediatrics. Sexually transmitted diseases in adolescents and children. In Kimberlin DW, Brady MT, Jackson MA, et al, eds. *2018 Red Book.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:170.

37. Is the size of the hymenal opening an important finding in the diagnosis of sexual abuse?

The hymenal opening is measured with a child in the supine, frog-leg position, and various studies have attempted to determine a size that most likely correlates with sexual abuse. The upper limit of normal had ranged from 4 to 8 mm, but variations in technique, positioning, and relative relaxation of the patient have rendered such measurements **generally unhelpful** and **nondiagnostic**. A more important part of the examination is inspection of the posterior hymen and surrounding tissues. Typically, a posterior rim of hymen measuring at least 1 mm is present unless there has been trauma. Complete transaction of the hymen leaves a permanent gap or defect. A full-thickness transaction through the posterior hymen (best visualized in the knee–chest position) is thought to be reliable evidence of trauma. Other variations of hymenal shape or size must be interpreted with caution because there is considerable overlap among abused and nonabused girls.

Berkoff MC, Zolotor AJ, Makoroff KL, et al. Has this prepubertal girl been sexually abused? *JAMA.* 2008;300(23):2779–2792.

Pillai M. Genital findings in prepubertal girls: what can be concluded from an examination? *J Pediatr Adolesc Gynecol.* 2008;21(4):177–185.

38. What is the most common finding of the physical examination of a child who has been sexually abused?

A **normal physical examination** is the most common physical finding, which is why in the absence of vaginal bleeding or other medical emergency, the physical examination should be deferred to an experienced medical examiner in a pediatric ED or a child advocacy center. It is crucial to know that a normal examination does not rule out sexual abuse.

39. What are the date-rape drugs?

Date-rape drugs are substances that render a patient incapable of saying "no" or asserting herself or himself, which makes it easier for a perpetrator to commit rape. The term typically applies to three drugs—**flunitrazepam** (*Rohypnol*), **γ-hydroxybutyrate** (*GHB*), and **ketamine hydrochloride**—which go by a variety of street names. The effects of these drugs, including somnolence, muscle relaxation, and profound sedation and amnesia—are enhanced by the concurrent use of alcohol.

40. How can you tell whether a patient has been given a date-rape drug?

Most of these drugs can be detected in blood and/or urine. However, because they are metabolized very quickly, it is important to screen early in your evaluation of the patient. For example, Rohypnol can be detected in blood for 24 hours and in urine up to 48 hours, GHB in urine only for up to 12 hours after ingestion, and ketamine in urine for up to 72 hours. None of these drugs is included in routine drug screen panels.

Kaufman M. Care of the adolescent sexual assault victim. *Pediatrics.* 2008;122(2):462–470.

KEY POINTS: FRACTURES OF ABUSE

1. Any fracture can be the result of nonaccidental trauma.
2. Critical in assessment: history, age of patient, developmental level of the patient, family history
3. Fractures with higher likelihood of abuse: rib, scapula, spinous process, sternum, long bone with metaphyseal lesions
4. Suspicious fractures: <18 months of age with humeral shaft fracture, complex or bilateral skull fractures, femoral fracture in nonambulatory child (without correlating history)
5. Skeletal surveys are indicated for suspected nonaccidental trauma in children <2 years of age.

KEY POINTS: RETINAL HEMORRHAGES

1. May be the only sign in an infant of a nonaccidental shaking injury
2. Almost never caused by seizures alone
3. Should always be assessed in an infant whose presenting symptoms include excessive irritability, lethargy, sepsis-like appearance, seizures, or coma
4. Should always be confirmed by an ophthalmologist
5. If found, should be followed by a skeletal series and cranial neuroimaging (CT scanning and/or MRI)

KEY POINTS: SEXUAL ABUSE

1. The most common physical finding is a normal examination.
2. The perpetrator is known to the victim in 75% to 80% of cases.
3. Infections that are diagnostic of abuse are gonorrhea, syphilis, chlamydia, and HIV.
4. For a prepubertal victim of sexual assault, NAAT is the preferred test for gonorrhea and chlamydia because a culture is too insensitive.
5. Reasons for immediate medical examination include ongoing bleeding or evidence of acute injury.
6. Use of accepted or standardized protocols is important during the evaluative process.

ENVIRONMENTAL INJURY

41. How do freshwater and saltwater drownings differ?

Fresh water injures the lung primarily by disrupting surfactant, thereby leading to alveolar collapse. Damage to the alveolar membranes leads to the transudation of fluid into the air spaces and pulmonary edema. *Salt water* pulls fluid into the air spaces directly by creating a strong osmotic gradient, and the accumulated water washes away surfactant, thereby leading to alveolar collapse. Both types result in abnormal surfactant function and increased capillary endothelial permeability. Patients develop ventilation-perfusion mismatch and hypoxemia, which may require aggressive mechanical support. Ultimately, management for either freshwater or saltwater drowning is the same.

Meyer RJ, Theodorou AA, Berg RA. Childhood drowning. *Pediatr Rev.* 2006;27(5):163–169.

42. How is the duration of submersion predictive of outcomes in drownings?

Risk for death or severe neurologic impairment after hospital discharge increases with duration of submersion as follows:

- 0 to 5 minutes: 10%
- 6 to 10 minutes: 56%
- 11 to 25 minutes: 88%
- $>$25 minutes: nearly 100%

  Signs of brainstem injury are also predictive of death or severe neurologic sequelae.

Szpilman D, Bierens JJ, Handley AJ, Orlowski. Drowning. *N Engl J Med.* 2012;366(22):2102–2110.

43. What cardiovascular changes occur as body temperature falls?

- **31°C to 32°C:** Elevated heart rate, cardiac output, and blood pressure; peripheral vasoconstriction and increased central vascular volume; normal electrocardiogram (ECG)
- **28°C to 31°C:** Diminished heart rate, cardiac output, and blood pressure; ECG irregularities include premature ventricular contractions (PVCs), supraventricular dysrhythmias, atrial fibrillation, and T-wave inversion
- **$<$28°C:** Severe myocardial irritability; ventricular fibrillation, usually refractory to electrical defibrillation; often absent pulse or blood pressure; J waves on ECG

44. What are the physiologic consequences of externally warming a severely hypothermic patient too rapidly?

- **Core temperature "after-drop":** The body temperature drops because external rewarming causes peripheral vasodilation and the return of cold venous blood to the core.
- **Hypotension:** Peripheral vasodilation increases total vascular space, thereby causing a drop in blood pressure.
- **Acidosis:** Lactic acid returns from the periphery, thereby resulting in rewarming acidosis.
- **Dysrhythmias:** Rewarming alters acid–base and electrolyte status in the setting of an irritable myocardium.

45. What are acceptable rewarming methods for the hypothermic child?

For patients with mild hypothermia (32°C to 35°C), passive rewarming by removing cold clothing and placing the patient in a warm, dry environment with blankets is generally sufficient. Active external rewarming involves the use of heating blankets, hot-water bottles, and overhead warmers and can also be used for patients with acute hypothermia in the 32°C to 35°C range. Active external rewarming should not be used for chronic hypothermia (>24 hours). More aggressive core rewarming techniques should be considered for patients with temperatures lower than 32°C. These techniques include gastric or colonic irrigation with warm fluids, peritoneal dialysis, pleural lavage, and extracorporeal blood rewarming with partial bypass. Intravenous and other fluids should be heated to 43°C. Patients should be given warmed, humidified oxygen by facemask or endotracheal tube (ETT).

Brown DJ, Brugger H, Boyd J, Paal P. Accidental hypothermia. *N Engl J Med.* 2012;367(2):1930–1938.

46. What organ systems are affected in patients suffering from heat stroke?

Heat stroke is a medical emergency of multisystem dysfunction that includes a very high body temperature (usually >41.5°C). The systems that are affected include the following:

- **Central nervous system (CNS):** confusion, seizures, and loss of consciousness
- **Cardiovascular:** hypotension as a result of volume depletion, peripheral vasodilation, and myocardial dysfunction
- **Renal:** acute tubular necrosis and renal failure, with marked electrolyte abnormalities
- **Hepatocellular:** injury and dysfunction
- **Heme:** abnormal hemostasis, often with signs of DIC
- **Muscle:** rhabdomyolysis

Jardine DS. Heat illness and heat stroke. *Pediatr Rev.* 2007;28(7):249–258.

47. How quickly can temperature rise inside an enclosed automobile?

The greatest rise in temperature in a closed vehicle occurs within the first 15 to 30 minutes. Leaving the window slightly open ("cracking the window") does not affect the rapid temperature elevation. In one observational study, the internal temperature of an automobile increased by ≈40°F compared with outside temperatures. Heat stroke is a significant cause of death in children who are left unattended in motor vehicles.

McLaren C, Null J, Quinn J. Heat stress from enclosed vehicles: moderate ambient temperatures cause significant temperature rise in enclosed vehicles. *Pediatrics.* 2005;116(1):e109–e111.

48. What are characteristics of heat stroke?

Heat stroke occurs when the body temperature exceeds 104°F, resulting in thermoregulatory collapse and accompanied by central nervous system (CNS) dysfunction. Symptoms include dizziness, disorientation, agitation, confusion, sluggishness, seizure, hot dry skin that is flushed but not sweaty, loss of consciousness, rapid heartbeat, and hallucinations. A core body temperature of 107°F or greater can be lethal because cells are damaged and internal organs begin to shut down.

McLaren C, Null J, Quinn J. Heat stress from enclosed vehicles: moderate ambient temperatures cause significant temperature rise in enclosed vehicles. *Pediatrics.* 2005;116(1):e109–e111.

49. Why are children more vulnerable to effects of external temperature changes?

Children's thermoregulatory systems are not as efficient as an adult's, and their body temperatures warm at a rate three to five times faster than an adult's.

50. What are the signs and symptoms of significant upper airway heat exposure in a patient who has been in a house fire?

- Carbonaceous sputum
- Singed nasal hairs
- Facial burns
- Respiratory distress

One should not rely on the presence of respiratory distress as an indicator for prompt endotracheal intubation. The first three signs listed represent significant heat exposure to the airway, and progressive swelling can rapidly progress to upper airway obstruction.

51. What are the signs and symptoms of impending respiratory failure as a result of mucosal injury and edema from heat exposure during a house fire?

- Hoarseness
- Stridor
- Increasing respiratory distress
- Drooling and difficulty swallowing

An ETT should be emergently considered for patients with these signs and symptoms. Upper airway mucosal swelling may make intubation difficult, and the most experienced physician should perform this intervention.

52. Which laboratory studies are needed for patients with suspected carbon monoxide (CO) poisoning?

- Blood carboxyhemoglobin (COHb) level
    - *0% to 1%:* Normal (smokers may have up to 5% to 10%)
    - *10% to 30%:* Headache, exercise-induced dyspnea, confusion
    - *30% to 50%:* Severe headache, nausea, vomiting, increased heart rate and respirations, visual disturbances, memory loss, ataxia
    - *50% to 70%:* Convulsions, coma, severe cardiorespiratory compromise
    - *70%:* Usually fatal
- **Hemoglobin level:** To evaluate correctable anemia
- **Arterial pH:** To detect acidosis
- **Urinalysis for myoglobin:** With CO poisoning, patients are susceptible to tissue and muscle breakdown with possible acute renal failure resulting from the renal deposition of myoglobin.

Macnow TE, Waltzman ML. Carbon monoxide poisoning in children: diagnosis and management in the emergency department. *Pediatr Emerg Med Pract.* 2016;13(9):1–24.

53. What are the key aspects of treatment for CO poisoning in children?

- Treatment includes **100% oxygen** through a nonrebreather mask until the COHb level falls to 5%. The half-life of COHb is 5 to 6 hours if the patient is breathing room air (at sea level). The half-life of COHb is reduced to 1 to 1.5 hours if the patient is breathing 100% oxygen (at sea level). The half-life of COHb is reduced to under 1 hour with hyperbaric oxygen therapy.
- Refer for use of **hyperbaric oxygen** for the following conditions: a history of coma, seizure, or abnormal mental status at the scene or in the ED; persistent metabolic acidosis; neonate; pregnancy (the fetus is more vulnerable to hypoxic effects of CO); or the COHb level is more than 25%, even if the patient is neurologically intact.

54. Why is CO such a deadly toxin?

- CO is **odorless** and **invisible** and can overwhelm a patient without warning.
- CO is **ubiquitous** as a product of partial combustion (car exhaust emissions, household heating equipment, burning charcoal).
- In the absence of a clear history, early CO intoxication is often **misdiagnosed** as a flulike illness.

55. What is the pathophysiology of CO poisoning?

- CO develops a **nearly irreversible bond with hemoglobin** (with an affinity 200 to 300 times that of oxygen) that shifts the oxyhemoglobin dissociation curve to the left and changes its shape from sigmoidal to hyperbolic (with greatly diminished O_2 tissue release).
- CO develops a **strong bond with other heme-containing proteins**, particularly in the mitochondria, thereby leading to metabolic acidosis and cellular dysfunction (especially in cardiac and CNS tissues).

56. What other serious exposure risk should one consider when managing a patient suffering from carbon monoxide poisoning?

One of the most important considerations in managing a CO-poisoned patient is concomitant **cyanide** (CN) poisoning. In CO-exposed patients with persistent acidosis and high lactate levels, one should seriously consider CN poisoning and treat accordingly. Supplemental oxygen therapy is not adequate. If CN poisoning is suspected, treat the patient with sodium thiosulfate.

Weaver LK. Carbon monoxide poisoning. *N Engl J Med.* 2009;360(12):1217–1225.

57. What are the different degrees of burn injuries?

See Table 5.2.

Table 5.2 Classification of Burn Wounds

DEGREE	DEPTH	CLINICAL APPEARANCE	CAUSE
Superficial	Epidermis	Dry, erythematous	Sunburn, scald
Partial	Superficial dermis	Blisters, moist, erythematous	Scald, immersion, contact
	Deep dermis	White eschar	Grease, flash fire
Full thickness	Subcutaneous	Avascular—white/dark, dry, waxy (yellow)	Prolonged immersion, flame, contact, grease, oil
	Muscle	Charred, skin surface cracked	Flame

Adapted from Coren CV. Burn injuries in children. *Pediatr Ann.* 1987;16:328-339.

58. How does the “rule of nines” apply in children?

The *“rule of nines”* is a tool used to estimate the extent of burns in adults. For example, in adults, the entire arm is 9% of the total body surface area (TBSA), the front of the leg is another 9% of the TBSA, and so on. The resulting estimate of the extent of burns is particularly helpful for calculating fluid requirements. Correction for age is necessary with this formula because of differing body proportions. Therefore, for children, use the surface of a patient’s palm, which represents about 1% of TBSA, as the tool for estimating the percentage of the TBSA affected by the burn (Fig. 5.5).

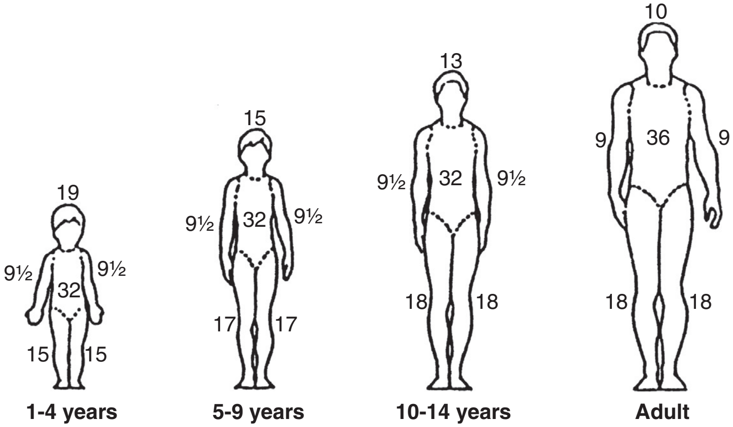

Fig. 5.5 Rule of nines as applied to children. (From Carvajal HF. Burn injuries. In Behrman RE ed. *Nelson Textbook of Pediatrics* 14th ed. Philadelphia, PA: W.B. Saunders; 1992:235.)

59. Which burn injuries are indications for hospitalization?

- Partial-thickness burns covering >10% of the TBSA
- Full-thickness burns covering >2% of the TBSA
- Significant burns involving the hands, feet, face, joints, or perineum
- Burns resulting from suspected child abuse
- Electrical burns
- Circumferential burns (which may predispose the patient to vascular compromise)
- Explosion, inhalation, or chemical burns (in which other organ trauma may be involved)
- Significant burns in children <2 years

Rodgers GL. Reducing the toll of childhood burns. *Contemp Pediatr.* 2000;17:152–173.

60. Why are alkali burns worse than acid burns in the eye?

Alkali burns are caused by lye (e.g., Drano, Liquid-Plumr), lime, or ammonia, in addition to other agents; they are characterized by liquefaction necrosis. They are worse than acid burns because the damage is ongoing. When spilled in the eye, acid is quickly buffered by tissue and limited in penetration by precipitated proteins; coagulation necrosis results, which is usually limited to the area of contact. Alkali, however, has a more rapid and deeper advancement, thereby causing progressive damage at the cellular level by combining with membrane lipids. This underscores the importance of extensive irrigation of the burned eye, particularly in cases of alkali burns.

61. How do the injuries produced by lightning and high-voltage wires differ?

- *Lightning:* Consists of direct current of extremely high voltage (200,000 to 2,000,000,000 volts) delivered over milliseconds. Lightning exposure causes massive electrical countershock with asystole, respiratory arrest, and minimal tissue damage.
- *High-voltage wires:* Deliver alternating current of lower voltage (rarely exceeding 70,000 volts) over a longer period. High-voltage exposure causes ventricular fibrillation and deep tissue injury. The resultant muscle necrosis can lead to substantial myoglobin release and renal failure.

62. In electrical injury, is alternating or direct current more hazardous?

At low voltages (e.g., those found in household electrical devices), **alternating current** is more dangerous than direct current. Exposure to alternating current can provoke tetanic muscle contractions so that the victim who has grasped an electrical source is unable to let go, thereby prolonging the exposure and producing greater tissue injury. Direct current or high-voltage alternating current typically causes a single forceful muscular contraction that will push or throw the victim away from the source.

63. What agents are the most common causes of anaphylaxis seen in U.S. emergency rooms?

Food. *Peanuts*, *tree nuts* (e.g., almonds, hazelnuts), and *seafood* head the list and are twice as common as bee stings as a trigger. Severe reactions occur 1 to 2 hours after exposure. Anaphylaxis may occur without a skin reaction, so a high index of suspicion is needed in a child with unexplained sudden bronchospasm, laryngospasm, severe GI symptoms, or poor responsiveness. In some adolescents, certain foods (e.g., wheat, celery, shellfish), if ingested within 4 hours of exercise, can lead to food-dependent, exercise-induced anaphylaxis. Risk factors for fatal anaphylactic reactions include a history of asthma, delayed diagnosis, and delayed administration of epinephrine.

Anagnostou K. Anaphylaxis in children: epidemiology, risk factors and management. *Curr Pediatr Rev.* 2018;14(3):180–186.

Rudders SA, Banerji A, Vassallo MF, et al. Trends in pediatric emergency department visits for food-induced anaphylaxis. *J Allergy Clin Immunol.* 2010;126(2):385–388.

64. What are important considerations when treating frostbite in children?

- Rewarm the affected area in water with a temperature of 37°C to 43°C (99°F to 109°F) for 20 minutes.
- Never attempt to rewarm if there is risk for refreezing.
- Rubbing the affected area may cause further damage to tissue.

KEY POINTS: ENVIRONMENTAL INJURIES

1. Food (e.g., peanuts, tree nuts, seafood) is twice as common as insect stings as a cause of anaphylaxis in children.
2. CO poisoning is often misdiagnosed because the presenting symptoms can be flulike.
3. Consider CN poisoning in patients with CO exposure. If there is persistent acidosis and high lactate, initiate therapy with sodium thiosulfate.
4. Impending upper airway obstruction in house fires is more likely if there is the presence of carbonaceous sputum, singed nasal or facial hairs, or respiratory abnormalities (e.g., hoarseness, stridor).
5. Hospitalization is indicated for significant burns involving the hands, feet, joints, or perineum or if there are circumferential burns.
6. Alkali burns are worse than acid burns because of ongoing liquefaction necrosis.

RESUSCITATION

65. Are there any indications for chest compression–only cardiopulmonary resuscitation (CPR) in children?

When trained medical personnel are present, such as with in-hospital arrests, simultaneous performance of chest compressions and ventilation is recommended for children and adults. However, new American Heart Association (AHA) guidelines encourage chest compressions alone for out-of-hospital arrest in adults if one or more lay rescuers are reluctant to perform mouth-to-mouth ventilation. However, **compression-only CPR is not recommended for children**. Ventilation remains vital for infants and children, as most arrests originate from a noncardiac nature with progressive tissue hypoxia and acidosis occurring due to respiratory failure or shock.

Atkins DL, de Caen AR, Berger S, et al. 2017 American Heart Association focused update on pediatric basic life support and cardiopulmonary resuscitation quality: an update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2018;137(1):e1–e6.

66. What common problems are identified in CPR done by professionals?

- Chest compressions are often too fast. Compressions should be done at a rate of 100 to 120 compressions per minute.
- Chest compression depth, which should be at least one-third of the depth of the child's chest, is often inadequately shallow, particularly when administered to younger children.
- Chest wall decompression (the relaxation phase) is often insufficient. Allow for full recoil.
- Ventilation rates are often excessive.

Niles DE, Duval-Arnould J, Skellett S, et al. Characterization of pediatric in-hospital cardiopulmonary resuscitation quality metrics across an international resuscitation collaborative. *Pediatr Crit Care Med.* 2018;19(5):421–432.

Sutton RM, Niles D, Nysaether J, et al. Quantitative analysis of CPR quality during in-hospital resuscitation of older children and adolescents. *Pediatrics.* 2009;124(2):494–499.

67. What is the role for capnography during resuscitation?

Capnography, the monitoring of carbon dioxide (CO_2), has been shown to be beneficial during CPR, as it may provide feedback on the effectiveness of chest compressions, although there are no specific pediatric data to show that it improves outcomes from cardiac arrest. When available, it should be utilized; however, the readings need to be interpreted cautiously, as vasoconstrictive medications, lung disease, and minute ventilation can affect the results.

Paiva EF, Paxton JH, O'Neil BJ. The use of end-tidal carbon dioxide (ETCO$_2$) measurement to guide management of cardiac arrest: a systematic review. *Resuscitation.* 2018;123:1–7.
de Caen AR, Berg MD, Chameides L, et al. Part 12: pediatric advanced life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2015;132(18 Suppl 2):S526–S542.

68. Why is the airway of an infant or child more prone to obstruction than that of an adult?

- Infants have **smaller airway diameters**. Because airflow is inversely proportional to the airway radius raised to the fourth power (Poiseuille's law), small changes in the diameter of the trachea can result in very large drops in airflow.
- The **tracheal cartilage** of an infant is **softer** and can collapse more easily if hyperextended.
- In an infant, the lumen of the oropharynx is relatively smaller due to the larger size of the tongue and smaller size of the mandible.
- **Lower airways** are **smaller and less developed** in children, thus putting them at risk for airway obstruction by small foreign bodies.

69. How can the correct size of ETTs be estimated for a given patient?

Pediatric Advanced Life Support guidelines now recommend that cuffed tubes be used in most children beyond the neonatal period. When choosing a *cuffed tube,* the formula [3.5 + (age in years / 4)] is most commonly used. Another guideline is that the child's pinky should approximate the internal diameter of the tube. When choosing an *uncuffed tube,* one should estimate one-half size larger, and the formula [4 + (age in years / 4)] is appropriate. Because these formulas are estimates, it is advisable to have tubes one-half size larger and smaller available and prepared before intubation.

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de Caen AR, Maconochie IK, Aickin R, et al. Part 6: pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation.* 2015;132(16 Suppl 1):S177–S203.

70. When should cuffed versus uncuffed ETTs be used?

In the past, uncuffed ETTs were recommended for children $<$8 years because of concern that the cuff could place excessive pressure on the already narrow portion of the pediatric cricoid cartilage. However, the AHA has advised that cuffed tubes are acceptable for infants and children undergoing emergent intubation. Cuffed tubes are now considered preferable in all children **beyond the neonatal period** and especially in those at high risk for aspiration, burn victims, and those with lung diseases that may necessitate higher ventilation pressures.

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de Caen AR, Maconochie IK, Aickin R, et al. Part 6: pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation.* 2015;132(16 Suppl 1):S177–S203.

71. How should the appropriate depth of an ETT be calculated?

After insertion of an ETT, the appropriate depth (measured from the gum line) may be approximated using the following formula for children older than 1 year: *(Age in years / 2) + 12 cm.* A shortcut calculation can be *diameter of the tube multiplied by 3*. These measurements should always be confirmed by clinical means and radiography.

72. How should correct placement of an ETT be confirmed?

- Adequate oxygen saturation
- Bilateral chest wall rise
- Bilateral symmetrical breath sounds
- Absence of gastric insufflation sounds over the stomach
- Use of an exhaled CO$_2$ detector device and continuous waveform capnography
- Direct laryngoscopy
- Chest radiography

73. What is a laryngeal mask airway (LMA)?

An *LMA* is an alternative device that can be used to ventilate children if the use of a bag-valve mask is unsuccessful and an ETT is unable to be placed. It consists of an inflatable silicone mask and rubber connecting tube. It is inserted blindly into the pharynx, forming a low-pressure seal around the laryngeal inlet and permitting gentle positive-pressure ventilation. It does not confer the same protection against aspiration as an ETT, nor is it as stable; however, in an emergency situation, it may be considered as a rescue device.

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de Caen AR, Maconochie IK, Aickin R, et al. Part 6: pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation.* 2015;132(16 Suppl 1):S177–S203.

74. What emergency drugs can be given through an ETT?

***L*idocaine, *E*pinephrine**, ***A*tropine**, ***N*aloxone** (**LEAN**). Vasopressin can also be administered through an ETT. However, if available, intraosseous or intravenous administration is always preferable because absorption is more predictable. The optimal dose of most drugs through the endotracheal route is not known. However, recommendations for epinephrine are 10 times the intravenous dose, and for other drugs, 2 to 3 times the intravenous dose. If drugs are being given through the ETT, they should be followed with 5 mL normal saline and positive-pressure ventilation.

Kleinman ME, de Caen AR, Chameides L, et al. Part 14: pediatric advanced life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2010;122:S876–S908.

Hähnel J, Lindner KH, Ahnefeld FW. Endobronchial administration of emergency drugs. *Resuscitation.* 1989;17(3):261–272.

75. What is the Sellick maneuver?

The *Sellick maneuver* is the application of pressure on the cricoid ring during rapid-sequence intubation to prevent aspiration. There is no clinical evidence that cricoid pressure reduces aspiration, and there is some evidence that it can make intubation more difficult by distorting the airway landmarks. If cricoid pressure is used during intubation, the AHA recommends that it be stopped if intubation or ventilation is difficult.

Bhatia N, Bhagat H, Sen I. Cricoid pressure: where do we stand? *J Anaesthesiol Clin Pharmacol.* 2014;30(1):3–6.

76. What are the potential reasons for acute deterioration in an intubated patient?

These can be remembered using the **DOPE** acronym:

- **D**isplacement of the ETT
- **O**bstruction of the ETT
- **P**neumothorax
- **E**quipment failure

American Heart Association. *PALS Provider Manual.* Dallas, TX: American Heart Association; 2016:169.

77. When is atropine indicated during CPR?

Atropine may be administered to the child with symptomatic bradycardia with a pulse after other resuscitative measures (i.e., oxygenation, ventilation, and epinephrine) have been initiated. Atropine may also be considered in cases of vagally induced bradycardia or anticholingergic poisoning. There is no evidence to support the routine use of atropine as a preintubation medication for critically ill infants. It may be used as a pre-intubation medication for patients who are at higher risk for bradycardia.

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de Caen AR, Berg MD, Chameides L, et al. Part 12: pediatric advanced life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2015;132(Suppl 2):S526–S542.

78. When is the use of calcium indicated during CPR?

Routine use of calcium is **generally not recommended** in resuscitation algorithms, as it has not been shown to improve return of spontaneous circulation. Calcium use may be considered in the following specific situations:

- Overdose of a calcium channel blocker
- Hyperkalemia resulting in cardiac dysrhythmia
- Documented hypocalcemia
- Hypermagnesemia
- Hyperkalemia

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de Caen AR, Maconochie IK, Aickin R, et al. Part 6: pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation.* 2015;132(16 Suppl 1):S177–S203.

79. What are contraindications to the use of an intraosseous line?

- Placement into a fractured bone
- Placement through dirty or infected skin
- Use in patients with bone disorders such as osteopetrosis or OI
- Repeat attempt into the same bone (due to risk for extravasation through the initial puncture site)

Burgert JM. A primer on intraosseous access: history, clinical considerations, and current devices. *Am J Disaster Med.* 2016;11(3):167–173.

80. Can laboratory tests be obtained from intraosseous lines?

Compared with venipuncture, there appears to be a good correlation between serum and marrow electrolytes, hemoglobin, drug levels, blood group typing, and renal function tests. Correlation is poorer with liver function tests and arterial blood gas studies (P_{CO_2} and P_{O_2}). Additionally, the positive correlations appear to worsen after 30 minutes

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of CPR and/or drug and fluid administration. The most reliable samples on which to base clinical decisions would be those obtained at the time of intraosseous line placement early in the resuscitation.

Blumberg SM, Gorn M, Crain EF. Intraosseous infusion: a review of methods and novel devices. *Pediatr Emerg Care.* 2008;24(1):50–56.

81. What are the complications of intraosseous lines?

Significant morbidity is very uncommon (<1%). The most common problems are extravasation of fluids and superficial skin infections. Osteomyelitis is rare (<0.6%) and typically only occurs with prolonged infusions. Other rare complications are skin necrosis, bone fractures, and compartment syndrome. Although there is the theoretical risk for significant bone growth arrest, growth plate damage, and fat embolism, these have not been reported. Obtaining venous access and discontinuing intraosseous infusions as soon as possible after stabilization have been recommended as means to further minimize complications.

Blumberg SM, Gorn M, Crain EF. Intraosseous infusion: a review of methods and novel devices. *Pediatr Emerg Care.* 2008;24(1):50–56.

82. What features indicate that an intraosseous needle has been correctly placed?

- A soft pop should be felt as you break through the cortex.
- The needle should feel very stable.
- There should be free flow of intravenous fluids without infiltration of subcutaneous tissues.
- Bone marrow aspiration, although confirming placement, may not always be possible even when needle placement is correct. Therefore, if you cannot aspirate marrow, you should rely on other signs for determination of placement.

83. How can a child's weight be estimated?

Some rules of thumb:

- An average term neonate weighs 3 kg.
- An average 1-year-old weighs 10 kg.
- An average 5-year-old weighs 20 kg.
- The following formula may also be used: $weight = (3 \times age) + 7$

Color-coded length-based tape measures, such as the Broselow tape, can also be used to estimate a child's weight. Guidelines suggest that in obese patients, medication doses should be calculated according to ideal body weight and should not be higher than recommended adult dosing.

Kleinman ME, de Caen AR, Chameides L, et al. Part 10: pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation.* 2010;122: S466–S515.

84. Name the potentially reversible causes of cardiac arrest.

- **H**s: **H**ypoxemia, **h**ypovolemia, **h**ypothermia, **h**yper/**h**ypokalemia, **h**ypoglycemia, and **h**ydrogen ion (acidosis)
- **T**s: **T**amponade, **t**ension pneumothorax, **t**oxins, and **t**hromboembolism

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American Heart Association. *PALS Provider Manual.* Dallas, TX: American Heart Association; 2016:166.

85. What are the typical clinical findings associated with supraventricular tachycardia (SVT)?

- Sudden onset
- Heart rate generally >180 beats per minute in children and >220 beats per minute in infants
- Minimal heart rate variability
- Absent, abnormal, or inverted P waves
- Infants: signs and/or symptoms that are usually nonspecific; however, if in SVT for hours or days, patients may present with signs/symptoms suggestive of congestive heart failure (CHF) or shock (e.g., poor feeding, irritability, vomiting, cyanosis, pallor, cough, respiratory distress, lethargy)
- Verbal children: palpitations and fluttering in the chest

Salerno JC, Seslar SP. Supraventricular tachycardia. *Arch Pediatr Adolesc Med.* 2009;163(3):268–274.

86. If an infant develops SVT, how long is it before CHF develops?

It is rare for an infant to develop CHF from SVT in less than 24 hours. When SVT is present for 24 to 36 hours, about 20% develop CHF. At 48 hours, the number increases to 50%.

Salerno JC, Seslar SP. Supraventricular tachycardia. *Arch Pediatr Adolesc Med.* 2009;163(3):268–274.

87. When should extracorporeal cardiac life support (extracorporeal membrane oxygenation [ECMO]) be considered?

ECMO may be considered in children when there is a monitored, witnessed cardiac arrest in a child with cardiac disease expected to recover or receive a tr[illegible]lant and the institution has the appropriate resources to initiate it

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rapidly. Extracorporeal CPR (E-CPR) is when ECMO is used in patients undergoing CPR. It may also be considered when dealing with pediatric cardiac arrest refractory to conventional interventions and when managing a reversible underlying disease process. This remains controversial.

Lasa JJ, Jain P, Raymond TT. Extracorporeal cardiopulmonary resuscitation in the pediatric cardiac population: in search of a standard of care. *Pediatr Crit Care.* 2018;19(2):125–130.

88. What factors may be predictive of outcomes after pediatric cardiac arrest?

Factors associated with improved likelihood of return of spontaneous circulation include:

- Short time to initiation of adequate CPR
- High-quality CPR
- Shorter overall duration of resuscitation
- Witnessed cardiac arrest

Factors associated with poor outcomes include:

- Infants
- Obesity
- Initial nonperfusing rhythm
- Out-of-hospital traumatic arrest

Kleinman ME, de Caen AR, Chameides L, et al. Part 10: pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation.* 2010;122:S466–S515.

89. Are fixed and dilated pupils a contraindication to resuscitation for a pediatric patient in cardiac arrest?

No. Pupillary dilation begins 15 seconds after cardiac arrest and is complete after about 1 minute and 45 seconds. It may only be a sign of transient hypoxia. The only absolute contraindications to resuscitation are rigor mortis, corneal clouding, dependent lividity, and decapitation.

90. When should a failing resuscitation be stopped?

Although there are no definitive guidelines, some studies have suggested that when **more than two rounds of epinephrine** have been given and/or >**20 minutes** have elapsed since the initiation of resuscitation without clinical cardiovascular or neurologic improvement, the likelihood of death or survival with neurologic devastation greatly increases. Unwitnessed out-of-hospital arrests are almost always associated with a poor outcome. In settings of hypothermia, patients should be rewarmed to 36°C before resuscitation is discontinued. In patients with acute, reversible conditions, such as drug toxicity or cardiac disease, extracorporeal cardiac life support may be considered if available.

American Heart Association. *PALS Provider Manual.* Dallas, TX: American Heart Association; 2016:185.
Schindler M, Bohn D, Cox PN, et al. Outcome of out-of-hospital cardiac or respiratory arrest in children. *N Engl J Med.* 1996; 335(20):1473–1479.

91. Why is resuscitation less successful in children than in adults?

Adults more commonly experience collapse and arrest from primary cardiac disease and associated dysrhythmias—ventricular tachycardia and fibrillation. These are more readily reversible and carry a better prognosis. *Children,* however, have cardiac arrest as a secondary phenomenon from other processes, such as respiratory obstruction or apnea, often associated with infection, hypoxia, acidosis, or hypovolemia. Primary cardiac arrest is rare. The most common dysrhythmia associated with pediatric cardiac arrest is asystole. It is less frequently reversible, and by the time a child has cardiac arrest, severe neurologic damage is almost always present.

SHOCK

92. Are all children in shock hypotensive?

No. Shock is an acute syndrome resulting from cardiovascular dysfunction that renders the circulatory system unable to provide oxygen to meet the metabolic demands of the body. In the initial stages of shock *(compensated shock)*, blood pressure is often preserved. Physiologically, children will maintain a state of compensated shock until very late in the progression of illness. Hypotension is commonly a terminal sign in septic shock.

93. What are the signs and symptoms of early or compensated shock?

- Unexplained tachycardia
- Mild tachypnea
- Delayed capillary refill
- Orthostatic changes in pressure or pulse
- Irritability

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94. What are the signs and symptoms of late or uncompensated shock?

- Increased tachycardia
- Increased tachypnea
- Poor peripheral pulses
- Capillary refill markedly delayed
- Cool extremities
- Hypotension
- Altered mental status
- Low urine output

95. How much blood volume can be lost before hypotension may be seen in children?

Some children can lose up to 30% of their blood volume before blood pressure noticeably declines. It is important to note that 25% of blood volume equals 20 mL/kg, which is only 200 mL in a 10-kg child. Losses >40% of blood volume cause severe hypotension that, if prolonged, may become irreversible.

96. What defines hypotension in children (i.e., systolic blood pressure <5th percentile for age)?

- Controversial in neonates and dependent on gestational age
- <70 mm Hg in infants
- <70 mm Hg + (2 × age in years) from ages 1 to 10 years
- <90 mm Hg in children >0 years

Kleinman ME, de Caen AR, Chameides L, et al. Part 14: pediatric advanced life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2010;122:S876–S908.

97. What types of shock can occur in children?

- **Hypovolemic:** Decreased circulating volume (blood loss, fluid loss from gastroenteritis; most common cause in children)
- **Distributive:** Pooling of blood in peripheral vasculature (septic, anaphylactic, neurogenic)
- **Cardiogenic:** Cardiac dysfunction with decreased cardiac output (e.g., congenital heart disease, myocarditis, dysrhythmia)
- **Obstructive:** Mechanical obstruction of ventricular outflow tract (e.g., cardiac tamponade, tension pneumothorax)

98. What are the differences between “warm” and “cold” septic shock?

- *Warm septic shock:* hyperdynamic response, characterized by increased cardiac output and decreased systemic vascular resistance; capillary refill time is brisk; pulses are full and bounding with widened pulse pressure (often from low diastolic pressure); warm, dry extremities; more common presentation in older children (and adults)
- *Cold septic shock:* hypodynamic response, characterized by decreased cardiac output and increased systemic vascular resistance; mottled or cold extremities with peripheral vasoconstriction; weak pulses on palpation; narrowed pulse pressure; underlying problem is impaired myocardial contractility; more common presentation in infants and young children

Differences in the clinical presentation of shock (“warm” versus “cold”) occur due to differing hemodynamic responses among patients to different pathologic causes of progression of sepsis.

Plunkett A. Sepsis in children. *BMJ.* 2015;350:h3017.
Brierley J, Peters MJ. Distinct hemodynamic patterns of septic shock at presentation to pediatric intensive care unit. *Pediatrics.* 2008;122(4):752–759.

99. When should vasoactive-intropic support be considered in the treatment of septic shock?

A key goal in the treatment of septic shock is the initiation of rapid fluid resuscitation. Initially, 20 mL/kg of isotonic crystalloid solution (either normal saline or lactated Ringer solution) is given as rapidly as possible. After the initial bolus, reassessment for signs of end-organ perfusion is vital, such as changes in the quality of pulses, capillary refill time, urine output, or mental status. Repeat 20 mL/kg boluses may be given, up to 60 mL/kg, with continued reassessment, including for signs of fluid overload, such as pulmonary rales. Within 1 hour, a judgment should be made if a patient is responding to fluid resuscitation. Patients who are deemed “fluid-refractory” should then be considered for the use of vasoactive-inotropic medications, with treatments differing between “cold” and “warm” shock.

Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine clinical practice for parameters for hemodynamic support of pediatric and neonatal septic shock. *Crit Care Med.* 2017;45(6):1061.

100. Are corticosteroids recommended for the treatment of septic shock?

There have been some studies in adults suggesting that corticosteroids may be beneficial for the treatment of septic shock. No large randomized controlled trial has been conducted in children. Currently, corticosteroids are recommended only for children who may have **fluid-resistant or catecholamine-resistant septic shock** or who have a **clear history or evidence of adrenal insufficiency**. An exception may be the neonate with vasopressor-resistant hypotension. Use of steroids has not been convincingly shown to impart survival advantage in children.

Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med.* 2018;46(9):1411–1420.

Menon K, McNally D, Choong K, Sampson M. A systematic review and meta-analysis on the effect of steroids in pediatric shock. *Pediatr Crit Care Med.* 2013;14(5):474–480.

101. What is the most important pharmacologic therapy for anaphylactic shock?

Epinephrine (1:1000 concentration). Epinephrine should be administered intramuscularly as soon as possible. Plasma concentrations of epinephrine appear to be highest when given intramuscularly in the thigh compared with subcutaneously or intramuscularly in the arm. If the patient has severe refractory symptoms and hypotension, epinephrine may be given as a continuous intravascular infusion. Failure to administer epinephrine quickly increases the risk for death from anaphylaxis.

Farbman KS, Michelson KA. Anaphylaxis in children. *Curr Opin Pediatr.* 2016;28(3):294–297.

102. What are the possible causes of shock in the newborn period?

The differential diagnosis is broad, but remember the mnemonic **THE MISFITS**:

- **T**rauma (nonaccidental and accidental)
- **H**eart disease and hypovolemia
- **E**ndocrine (e.g., congenital adrenal hyperplasia)
- **M**etabolic (electrolyte)
- **I**nborn errors of metabolism
- **S**epsis (e.g., meningitis, pneumonia, urinary tract infection)
- **F**ormula mishaps (e.g., underdilution or overdilution)
- **I**ntestinal catastrophes (e.g., volvulus, intussusception, necrotizing enterocolitis)
- **T**oxins and poisons
- **S**eizures

Brousseau T, Sharieff GQ. Newborn emergencies: the first 30 days of life. *Pediatr Clin N Am.* 2006;53(1):69–84.

103. A 4-day-old infant presents to the ED in shock with evidence of CHF and cyanosis. In addition to managing the airway and breathing, what is the first line of pharmacologic therapy?

This baby likely has congenital heart disease with a ductal-dependent lesion, such as hypoplastic left heart syndrome or coarctation of the aorta. The baby will require **prostaglandin E_1** infusion to maintain the patency of the ductus arteriosus until corrective surgery can be performed. If possible, an echocardiogram should be urgently performed because some congenital heart lesions will worsen when prostaglandin E_1 is infused.

104. What are the four classes of medications that can be used to support cardiac output?

- **Inotropes:** Increase cardiac contractility and often heart rate (e.g., dopamine, dobutamine, epinephrine)
- **Vasopressors:** Increase vascular resistance and blood pressure (e.g., higher-dose dopamine, epinephrine, norepinephrine, vasopressin)
- **Vasodilators:** Decrease vascular resistance and cardiac afterload and promote peripheral perfusion (e.g., sodium nitroprusside)
- **Inodilators:** Increase cardiac contractility and reduce afterload (e.g., milrinone)

105. An 8-year-old presents to the ED after falling head-first into an empty swimming pool. His heart rate is normal, yet despite aggressive fluid resuscitation he remains hypotensive. CT scans of the chest, abdomen, pelvis, and head reveal only a small cerebral contusion. What is the likely cause of his hypotension?

This patient is most likely suffering from **neurogenic shock.** Loss of sympathetic tone prevents the expected tachycardic response. The hallmarks of neurogenic shock are hypotension with either bradycardia or a normal heart rate despite fluid replenishment. If the hypotension cannot be corrected with fluid expansion, vasopressor therapy may be required and, within the first 8 hours, corticosteroids may be considered.

KEY POINTS: SIGNS AND SYMPTOMS OF SHOCK

1. Tachycardia
2. Poor peripheral pulses
3. Slow capillary refill
4. Cool extremities
5. Hypotension
6. Altered mental status

KEY POINTS: SHOCK IN PEDIATRIC TRAUMA

1. Shock in pediatric trauma patients is often masked because the inherent reserve in a child allows for the maintenance of vital signs for a long period, even in the presence of severe hemodynamic compromise.
2. Shock should be suspected in patients with tachycardia, a decrease in pulse pressure >20 mm Hg, skin mottling, cool extremities, delayed capillary refill (>2 seconds), and altered mental status.
3. The presence of hypotension in a child represents a state of uncompensated shock and indicates severe blood loss.
4. Shock is not explainable by head trauma alone, except in the case of an infant with open fontanels and unfused cranial sutures, who may have a significant hemorrhage into the subgaleal space.
5. Shock may be associated with femur and/or pelvic fractures.
6. Shock should quickly prompt an evaluation of the child's abdomen for a possible source of blood loss.

TOXICOLOGY

106. What are common poisonings in children younger than 6 years?

See Table 5.3.

Table 5.3 Common Poisonings in Children

NONPHARMACEUTICALS	PHARMACEUTICALS
Cosmetics and personal care products	Analgesics
Cleaning substances	Cough and cold preparations
Plants, including mushrooms and tobacco	Topical agents
Battery, toys, and other foreign bodies	Vitamins
Insecticides, pesticides, and rodenticides	Antimicrobials

107. Which medications can kill a 10-kg toddler with 1 or 2 tablets, capsules, or teaspoonfuls?

- **Tricyclic antidepressants** (amitriptyline, imipramine, desipramine)
- **Antipsychotics** (thioridazine, chlorpromazine)
- **Antimalarials** (chloroquine, hydroxychloroquine)
- **Antiarrhythmics** (procainamide, flecainide)
- **Calcium channel blockers** (nifedipine, verapamil)
- **Oral hypoglycemics** (glyburide, glipizide)
- **Opioids** (methadone, hydrocodone)
- **Imidazolines** (clonidine, tetrahydrozoline)

Bar-Oz B, Levichek Z, Koren G. Medications that can be fatal for a toddler with one tablet or teaspoonful. *Paediatr Drugs.* 2004; 6(2):123–126.

108. Name the toxicology "time bombs."

Time bombs are medications that lack symptoms early after ingestion but later have a profoundly toxic course.

- **Acetaminophen** (delayed hepatic injury)
- **Iron** (delayed cyanosis and profound metabolic acidosis)
- **Alcohols**—methanol (delayed acidosis), ethylene glycol (delayed nephrotoxicity)
- **Lithium** (delayed neurologic symptoms due to late CNS drug penetration)
- **Anticonvulsants**—phenytoin (Dilantin), carbamazepine
- **Time-release medications**

109. What empirical drug therapies are indicated for the poisoned child who presents with altered mental status?

All poisoned patients with depressed mental status should receive *oxygen* through a nonrebreather facemask. Blood glucose should be rapidly evaluated or empirical treatment for hypoglycemia initiated with **intravenous glucose**, 0.5 g/kg. Hypoglycemia is associated with ingestion of ethanol, beta blockers, and oral hypoglycemic agents. **Naloxone** should be given as a diagnostic and therapeutic measure in the event of suspected or known opioid ingestion.

110. What is GI decontamination?

GI decontamination refers to a variety of medications that may be administered and techniques that may be used to decrease the absorption of ingested poisons. Methods of GI decontamination include activated charcoal, whole-bowel irrigation (WBI), and gastric lavage. The effectiveness of these techniques is difficult to study, and much of the available evidence is based on animal and volunteer studies.

Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. *Clin Toxicol (Phila).* 2013;51(3):140–146.

111. How does single-dose activated charcoal work, and when should it be considered?

Single-dose activated charcoal is prepared as a liquid slurry and given orally to a poisoned patient. As it enters the stomach, it adsorbs toxins, thereby preventing absorption into the circulation. It is most efficacious when given as early as possible after ingestion. The “1-hour” rule is rarely used now because there is evidence that in overdose, there is delayed gastric emptying and pills often sit around in the stomach for a while. Single-dose activated charcoal will likely be beneficial for most ingestions if there is no contraindication. Charcoal is contraindicated in patients whose airway reflexes are compromised, and it should not be given through nasogastric tube unless the airway is protected with an ETT because of the risk for aspiration.

Juurlink DN. Activated charcoal for acute overdose: a reappraisal. *Br J Clin Pharmacol.* 2016;81(3):482–487.

112. Should activated charcoal be given to a sleepy 2-year-old girl who consumed half a bottle of a liquid antihistamine 2 hours before evaluation?

No. This child has a potentially compromised airway because of her altered mental status. In addition, the effectiveness of activated charcoal is known to decrease rapidly with time. Therefore in this clinical scenario, the risks of administering charcoal and potentially causing vomiting and aspiration outweigh the benefits.

113. For what substances is charcoal not recommended?

- **Hydrocarbons**, because of possible increased risk for aspiration
- **Others**: acids, alcohols, alkalis, cyanide, iron, heavy metals, and lithium

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American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. Position statement: single-dose activated charcoal. *J Toxicol Clin Toxicol.* 2005;43:61–87.

114. When is gastric lavage indicated?

Gastric lavage involves the passage of a large orogastric tube (e.g., 24-Fr orogastric for a toddler, 36-Fr orogastric for a teenager) with sequential administration and aspiration of small volumes of normal saline (10 mL/kg in a child; 200 to 300 mL in an adult) with the intent of removing toxic substances present in the stomach. Efficacy remains unproved, and complications are significant (e.g., laryngospasm, esophageal injury, aspiration pneumonia); it should not be used routinely. A position paper by the American Academy of Clinical Toxicology (AACT) and European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) indicates that there is no evidence showing that gastric lavage should be used routinely, if at all, in the management of poisonings. Evidence for use in special situations (e.g., lethal ingestions, recent exposures, substance not bound to activated charcoal) is weak. If performed by well-practiced physicians, it may be considered for patients with a life-threatening quantity of a poisonous ingestion occurring within 60 minutes of evaluation if the patient’s airway is protected.

Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. *Clin Toxicol.* 2013; 51(3):140–146.

115. What are the indications for WBI in acute ingestions?

This is a method of GI decontamination using a large volume of polyethylene glycol–balanced electrolyte solution such as GoLYTELY given by mouth or nasogastric tube. These solutions are not known to cause electrolyte imbalance because they are neither significantly absorbed nor do they exert osmotic effect. WBI may be considered for toxic ingestions of sustained-release or enteric-coated medications. It may also be helpful in ingestions of large amounts of iron or packets of illicit drugs. The most important contraindication to WBI is airway compromise. Although WBI may be helpful for those who have ingested heavy metals (e.g., lead) or long-acting or sustained-release medications, there are few clinical trials about the effectiveness of this procedure in children.

Thanacoody R, Caravati EM, Troutman B, et al. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. *Clin Toxicol (Phila).* 2015;53(1):5–12.

116. How is the manipulation of urinary pH used in treating poisonings?

Alkalinization of the urine is considered valuable in the management of acute overdoses of salicylates, barbiturates, or tricyclic antidepressants. **Acidification** is rarely, if ever, used for treating poisonings because of potential complications from fluid overload, risk for acidemia, and availability of other therapeutic options (e.g., hemodialysis).

117. What ingestions and exposures have available antidotes?

See Table 5.4.

Table 5.4 Antidotes

INGESTION OR EXPOSURE	ANTIDOTE
Acetaminophen	*N*-acetylcysteine (Mucomyst)
Anticholinergics	Physostigmine
Benzodiazepines	Flumazenil
Beta blockers	Glucagon
Carbon monoxide	Hyperbaric oxygen chamber
Calcium channel blocker	Calcium, glucagon
Cyanide	Sodium nitrite, sodium thiosulfate
Digoxin	Digibind (antidigoxin antibody)
Ethylene glycol	Ethanol, fomepizole
Iron	Deferoxamine
Isoniazid	Pyridoxine (vitamin B_6)
Lead	EDTA, DMSA
Mercury	Dimercaprol, DMSA
Methanol	Ethanol
Methemoglobinemic agents	Methylene blue
Opiates	Naloxone, nalmefene
Organophosphates	Atropine, pralidoxime
Phenothiazines (dystonic reaction)	Diphenhydramine
Tricyclics	Bicarbonate
Warfarin (rat poison)	Vitamin K

DMSA, Dimercaptosuccinic acid; *EDTA,* ethylenediaminetetraacetic acid.

118. For which kinds of ingestions is naloxone considered an antidote?

Naloxone (Narcan) is an antidote for opioid drugs. It reverses the CNS and respiratory depression of morphine and heroin and clears the depressed sensorium in overdoses due to many of the synthetic opioids, including propoxyphene, codeine, dextromethorphan, pentazocine, and meperidine. It is also a known antidote for clonidine, although it may be inconsistent in its efficacy.

119. Which ingestions are radiopaque on abdominal radiograph?

The mnemonic **CHIPS** indicates possible suspects:

- **C**hloral hydrate
- **H**eavy metals (arsenic, iron, lead)
- **I**odides
- **P**henothiazines, psychotropics (cyclic antidepressants)

- **S**low-release capsules, enteric-coated tablets

The likelihood of radiopacity depends on numerous factors, including weight of the patient, size of the ingestion, and composition of the pill matrix.

Barkin RM, Kulig KW, Rumack BH. Poisoning and overdose. In Barkin RM, Rosen P, eds. *Emergency Pediatrics*. 4th ed. St. Louis, MO: Mosby; 1994:335.

120. What causes the radiographic "lead lines" of chronic lead poisoning?

Lead lines are transverse metaphyseal bands most prominent at the end of longer tubular bones, which are seen in the later stages of chronic lead exposure (Fig. 5.6). They represent **increased calcium** (not lead) **deposits**. Excessive lead interferes with bone metabolism and disrupts the resorption of primary spongiosa bone by disproportionately disrupting osteoclasts, which are involved in bone disassembling, compared with osteoblasts, which participate in calcium deposition. As a result of lead toxicity and relative increased osteoblastic activity, there is an exuberant calcium deposition that results in the dense metaphyseal bands corresponding to the zone of provisional calcification.

Raber SA. The dense metaphyseal band sign. *Radiology.* 1999;211(3):773–774.

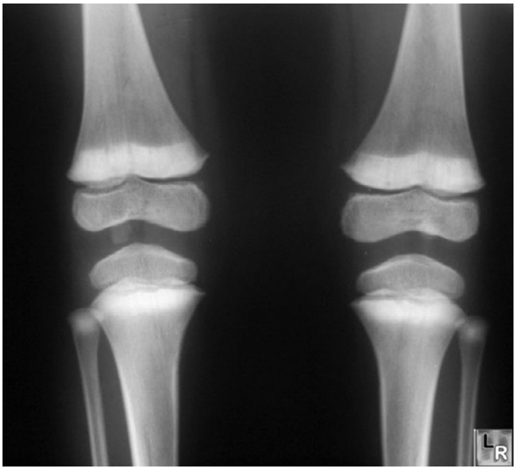

Fig. 5.6 Long-bone radiograph of both knees of a child with lead poisoning showing dense metaphyseal bands involving the distal femurs, proximal tibias, and proximal fibulas. (From Dapul H, Laraque D. Lead poisoning in children. *Adv Pediatr*. 2014:61:313-333.)

121. What is a toxidrome?

A *toxidrome,* short for a toxic syndrome, is a clinical constellation of signs and symptoms that is very suggestive of a particular poisoning or category of intoxication.

Koren G. A primer of paediatric toxic syndromes or "toxidromes." *Paediatr Child Health.* 2007;12(6):457–459.

122. What is the toxidrome for anticholinergics?

The classic description of anticholinergic toxicity is "mad as a hatter, fast as a hare, red as a beet, dry as a bone, blind as a bat, full as a flask, hot as Hades."

- *Hatter*: delirium, visual hallucinations
- *Hare*: tachycardia, hypertension
- *Beet*: flushed skin, facial flushing
- *Bone*: dry skin, dry mucous membranes
- *Bat:* dilated, sluggish pupils
- *Flask*: urinary retention, decreased GI motility, hypoactive bowel sounds
- *Hades*: hyperpyrexia, inability to sweat

123. What breath odors may be associated with specific ingestions?

See Table 5.5.

Woolf AD. Poisoning in children and adolescents. *Pediatr Rev.* 1993;14(11):411–422.

Table 5.5 Breath Odors Associated With Specific Ingestions

CHARACTERISTIC ODOR	RESPONSIBLE TOXIN OR DRUG
Wintergreen	Methyl salicylate
Bitter almond	Cyanide
Carrots	Cicutoxin (of water hemlock)
Fruity	Ethanol, acetone (nail polish remover), isopropyl alcohol, chloroform
Fishy	Zinc or aluminum phosphide
Garlic	Organophosphate insecticide, arsenic, thallium
Glue	Toluene
Minty	Mouthwash, rubbing alcohol
Mothballs	Naphthalene, *p*-dichlorobenzene, camphor
Peanuts	Vacor rat poison (odor is from a flavoring agent)
Rotten eggs	Hydrogen sulfide, *N*-acetylcysteine, disulfiram
Rope (burned)	Marijuana, opium
Shoe polish	Nitrobenzene

124. What are the limitations of the routine toxicology screen?

Most toxicology screens are intended to detect drugs encountered in substance abuse. A positive drug screen, however, is not necessarily indicative of current use; some drugs can be detected for several days or weeks. Even in large pediatric hospitals, comprehensive toxicology screens generally include only a fraction of drugs available to children. Most blood screens analyze for acetaminophen, salicylates, and alcohols. Urine is often screened for substances of abuse and other common psychoactive drugs, including antidepressants, antipsychotics, benzodiazepines, sedative-hypnotics, and anticonvulsants. Other potential toxins that can cause mental status changes (carbon monoxide, chloral hydrate, cyanide, organophosphates) or circulatory depression (beta blockers, calcium channel blockers, clonidine, digitalis) may not be included but may be assayed through individual blood tests. In clinical studies, toxicology screens are most valuable in quantitative settings (i.e., assessing drug levels). Additionally, treatment of the acutely poisoned patient must begin long before the results of many toxicology screens are available.

Moeller KE, Kissack JC, Atayee RS, et al. Clinical interpretation of urine drug tests: what clinicians need to know about urine drug screens. *Mayo Clin Proc.* 2107;92(5):774–796.

Archer JRH, Wood DM, Bargan PI. How to use toxicology screening tests. *Arch Dis Child Educ Pract Ed.* 2012;97(5):194–199.

125. After use of marijuana, how long does a urine screen remain positive?

After first-time single use, the drug screen can be positive for 3 days. A long-term heavy marijuana user can have a positive drug test that may persist ≥30 days after cessation. Two cautions: although rare, nonsteroidal medications, including ibuprofen, and proton pump inhibitors have been reported to cross-react with cannabinoid immunoassays. In addition, false-negative results can occur if a wise teen adds Visine eye drops to a urine specimen. The chemicals in Visine directly lower the concentrations of the cannabinoids in the urine.

Moeller KE, Kissack JC, Atayee RS, et al. Clinical interpretation of urine drug tests: what clinicians need to know about urine drug screens. *Mayo Clin Proc.* 2017;92(5):774–796.

126. How do the types of alcohol ingestions vary?

All alcohols can cause CNS disturbances ranging from mild mentation and motor abnormalities to respiratory depression and coma. Each alcohol is associated with specific metabolic complications:

- **Ethanol** (present in beverages, colognes and perfumes, aftershave lotion, mouthwash, topical antiseptic, rubbing alcohol) in infants and toddlers can cause the classic triad of coma, hypothermia, and hypoglycemia, and in adolescents can cause intoxication and mild neurologic findings. At levels higher than 500 mg/dL, it can be lethal.
- **Methanol** (present in antifreeze and windshield washer fluid) can cause severe, refractory metabolic acidosis and permanent retinal damage leading to blindness.

- **Isopropyl alcohol** (present in jewelry cleaners, rubbing alcohol, windshield deicers, cements, paint removers) can cause gastritis, abdominal pain, vomiting, hematemesis, CNS depression, moderate hyperglycemia, hypotension, and ketosis without acidosis.
- **Ethylene glycol** (present in antifreeze, brake fluid) causes severe metabolic acidosis. In addition, it is metabolized to oxalic acid, which can cause renal damage by the precipitation of calcium oxalate crystals in the renal parenchyma and can lead to hypocalcemia.

127. Which alcohol is considered the most lethal?

Methanol. Deaths can arise from doses as little as 4 mL of pure methanol. Unique to methanol is that it becomes more toxic as it is metabolized. Methanol is broken down by alcohol dehydrogenase to formaldehyde and formic acid. It is the formic acid that causes the refractory metabolic acidosis and ocular symptoms.

128. What is the treatment for methanol and ethylene glycol ingestions?

Both methanol and ethylene glycol require the enzyme alcohol dehydrogenase to create their toxic metabolites. Ethanol (as an antidote) competitively inhibits the formation of these metabolites by serving as a substrate for the enzyme. However, it is inebriating, may cause hypoglycemia, and its kinetics are widely variable. **Fomepizole** is a safer and more effective blocker of alcohol dehydrogenase.

McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. *Br J Clin Pharmacol.* 2016; 81(3):505–515.

129. What is "MUDPILES"?

MUDPILES is a mnemonic for ingestions associated with a **high anion gap metabolic acidosis**.

- **M**ethanol, metformin
- **U**remia
- **D**iabetic ketoacidosis
- **P**araldehyde
- **I**soniazid, iron, inborn errors of metabolism
- **L**actic acidosis (seen with shock, CO, cyanide)
- **E**thanol, ethylene glycol
- **S**alicylates

130. How can pupillary findings assist in the diagnosis of toxic ingestions?

- **Miosis** (pinpoint pupils): opioids, organophosphates, phencyclidine, clonidine, phenothiazines, barbiturates, ethanol
- **Mydriasis** (dilated pupils): anticholinergics (atropine, antihistamines, cyclic antidepressants); sympathomimetics (amphetamines, caffeine, cocaine, lysergic acid diethylamide [LSD], nicotine)
- **Nystagmus:** barbiturates, ketamine, phencyclidine, phenytoin

131. If a child has ingested an acetaminophen-containing product, when should the first acetaminophen level be obtained?

A plasma level obtained **4 hours** after ingestion is a good indicator of the potential for hepatic toxicity. Nomograms are available for determining risk. As a rule, doses under 150 mg/kg are unlikely to be harmful.

132. When should a "NAC attack" begin?

N-acetylcysteine (NAC) is a specific antidote for acetaminophen hepatotoxicity by serving as a glutathione substitute in detoxifying the hepatotoxic metabolites. It is of greatest benefit to reduce hepatotoxicity when administered **<8 to 10 hours after acetaminophen overdose**. It should be used for any acetaminophen overdose with a toxic serum acetaminophen level (based on the nomogram) or any patient with signs of hepatotoxicity. If acetaminophen levels are not available on a rapid basis or the time since ingestion is not clear, it is preferable to initiate NAC.

133. How does NAC prevent hepatotoxicity in acetaminophen overdose?

Normally, 94% of acetaminophen is metabolized to glucuronide or sulfate form and 2% is excreted unchanged in urine, both of which are nontoxic. The remaining 4% is conjugated with glutathione (with the help of cytochrome P-450) to form mercapturic acid, which is also not hepatotoxic. When a significant acetaminophen overdose occurs, cytochrome P-450 becomes the major system for metabolizing the acetaminophen, leading to depletion of hepatic stores of glutathione. When the glutathione is depleted to less than 70% of normal, a highly reactive intermediate metabolite binds to hepatic macromolecules, causing hepatocellular necrosis. It is presumed that NAC replenishes the glutathione, thus helping the cytochrome P-450 in converting the excess acetaminophen into mercapturic acid.

Wong A, Graudins A. Risk prediction of hepatotoxicity in paracetamol poisoning. *Clin Toxicol (Phila).* 2017;55(8):879–892.
Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med.* 2008;359(3):285–292.

134. What arterial blood gas pattern is classic for salicylate poisoning?

Metabolic acidosis and **respiratory alkalosis.** Salicylates directly stimulate the medullary respiratory drive center, causing tachypnea with diminished P_{CO_2} (respiratory alkalosis). They also cause lactic acidosis and ketoacidosis by inhibiting Krebs cycle enzymes, uncoupling oxidation phosphorylation, and inhibiting amino acid metabolism (metabolic acidosis).

135. What are hidden salicylates?

These are salicylates that are found in over-the-counter products, such as Pepto-Bismol (bismuth salicylate). Salicylate absorption can be substantial, and in the setting of influenza or chickenpox, Pepto-Bismol use has been discouraged because of the potential for complications such as the development of Reye syndrome, a rare, rapidly progressive encephalopathy.

Szap MD. Hidden salicylates. *Am J Dis Child.* 1989;143(2):142.

136. What are the classic ECG findings associated with tricyclic antidepressants?

Tricyclic antidepressants interfere with myocardial conduction and can precipitate **ventricular tachycardias** or **complete heart block**. A QRS interval >0.1 second is predictive of poor outcome in these patients. The presence of a **large R wave in lead aVR** is also associated with tricyclic antidepressants. If these findings are noted, treatment with sodium bicarbonate should be initiated. Sodium bicarbonate helps prevent the sodium channel blockade that is caused by these medications. Of note, diphenhydramine (Benadryl), if ingested in high doses, can mimic the ECG findings of tricyclic antidepressants.

137. Which clinical and laboratory features correlate with an acutely elevated serum iron?

Serum iron levels obtained 4 to 6 hours after ingestion correlate with severity of toxicity. Iron levels >300 μg/dL are associated with mild toxicity consisting of local GI symptoms, such as nausea, vomiting, and diarrhea. A serum iron level of 500 μg/dL is associated with serious systemic toxicity, and a level of 1000 μg/dL is associated with death. Other laboratory tests that correlate with an elevated iron level include leukocytosis (>15,000/mm^3) and hyperglycemia (>150 mg/dL). Sometimes, radiopaque tablets may be demonstrated on abdominal radiograph.

Chang TP, Rangan C. Iron poisoning: a literature-based review of epidemiology, diagnosis, and management. *Pediatr Emerg Care.* 2011;27(10):978–985.

138. What are the four clinical stages of iron toxicity and the correlating pathophysiology?

- **Stage 1** *(0.5 to 6 hours)*: During this stage, iron exhibits a direct corrosive effect on the small bowel. Symptoms include nausea, vomiting, abdominal pain, and/or GI hemorrhage.
- **Stage 2** *(6 to 24 hours)*: Iron accumulates in the mitochondria; the patient is relatively symptom free.
- **Stage 3** *(4 to 40 hours)*: This phase is characterized by systemic toxicity with shock, metabolic acidosis, depressed cardiac function, and hepatic necrosis.
- **Stage 4** *(2 to 8 weeks)*: During this phase, pyloric stenosis and obstruction can develop as a result of earlier local bowel irritation.

139. When can a toddler who may have swallowed some multivitamins be discharged home?

The toxic compound in multivitamin overdose is iron. A large variety of children's chewable multivitamins contain different amounts of elemental iron (0 to 18 mg of elemental iron per tablet). The toxic dose of iron ingestion is at least 20 mg/kg of elemental iron, and the lethal dose of iron reported is in the range of 60 to 180 mg/kg of elemental iron. In a small child, a toxic dose is about 300 mg of elemental iron, which is the equivalent of 20 tablets of multivitamins containing 15 mg/tab of elemental iron. Frequently, the amount of ingestion is not known. Because iron can initially cause nausea, vomiting, or abdominal pain, a child with a suspected but unknown amount of iron poisoning can be observed, and an iron level may be obtained. A child who has no complaints and has a normal physical examination after 4 to 6 hours of observation can be safely discharged home.

140. How do alkaline and acidic household products vary in their toxicity after an ingestion?

Both can cause severe esophageal and airway burns upon ingestion, but by different mechanisms. *Alkali-based* household products (such as concentrated laundry or dishwasher detergents, including single-use capsules or pods with colorful packaging particularly enticing to children <5 years of age) cause injury by **liquefaction necrosis**. This type of necrosis involves dissolving proteins and lipids, thereby allowing deeper penetration of the caustic substance with greater local tissue injury. With ingestion of *acid-based* products (such as concentrated toilet bowl cleaners), **coagulation necrosis** of the tissue occurs. This results in the formation of an eschar that limits the penetration of the toxin into deeper tissues.

141. Which hydrocarbons pose the greatest risk for chemical pneumonitis?

The household hydrocarbons with **low viscosities** pose the greatest aspiration hazard. These include furniture polishes, gasoline and kerosene, turpentine and other paint thinners, and lighter fuels.

142. What is the differential diagnosis in a child who presents with confusion and lethargy?

An altered state or level of consciousness can be due to many causes.

The mnemonic **AEIOU TIPS** encompasses the many possible causes:

- **A**lcohol, abuse of substances
- **E**pilepsy, encephalopathy, electrolyte abnormalities, endocrine
- **I**nsulin, intussusception
- **O**verdose, oxygen deficiency
- **U**remia
- **T**rauma, temperature abnormality, tumor
- **I**nfection
- **P**oisoning, psychiatric conditions
- **S**hock, stroke, space-occupying lesion (intracranial)

Avner JR. Altered states of consciousness. *Pediatr Rev.* 2006;27(9):331–337.

143. A patient receiving an antiemetic drug (e.g., promethazine) who develops involuntary, prolonged, twisting, writhing movements of the neck, trunk, and arms likely has what condition?

Acute dystonia. This dystonic reaction is classically seen as an adverse side effect of antidopaminergic agents such as neuroleptics, antiemetics, or metoclopramide. In children, phenothiazines are the most common culprit. Treatment includes administration of diphenhydramine (Benadryl). Benztropine (Cogentin) is also used in adolescents.

144. What do “SLUDGE” and “DUMBELS” have in common?

Both are mnemonics used to remember the problems involved with **organophosphate poisoning**, including lipid-soluble insecticides used in agriculture and terrorism (“nerve gas”). Organophosphates *inhibit cholinesterase* and cause all the signs and symptoms of acetylcholine excess.

- *Muscarinic effects* are increased oral and tracheal secretions, miosis, salivation, lacrimation, urination, vomiting, cramping, defecation, and bradycardia; may progress to frank pulmonary edema. Think killer Bs (bradycardia, bronchospasm, bronchorrhea).
- *CNS effects* are agitation, delirium, seizures, and/or coma.
- *Nicotinic effects*: Sweating; muscle fasciculation; and ultimately, paralysis
- The mnemonic *SLUDGE* is **s**alivation, **l**acrimation, **u**rination, **d**efecation, **G**I cramps, and **e**mesis.
- The mnemonic *DUMBELS* is **d**efecation, **u**rination, **m**iosis, **b**ronchorrhea/bradycardia, **e**mesis, **l**acrimation, and **s**alivation.

145. What metal intoxication can mimic Kawasaki disease?

Mercury. *Acrodynia* is the term applied to one form of mercury salt intoxication that results in a constellation of signs and symptoms very similar to that currently recognized as Kawasaki disease. The classic presentation of acrodynia was described in children exposed to calomel, a substance used in teething powders, which was essentially mercurous chloride. The symptom complex included swelling and redness of the hands and feet, skin rashes, diaphoresis, tachycardia, hypertension, photophobia, and an intense irritability with anorexia and insomnia. Infants were often very limp, lying in a froglike position, with impressive weakness of the hip and shoulder girdle muscles. Similar symptoms have been described in children exposed to other forms of mercury, including broken fluorescent light bulbs or diapers rinsed in mercuric chloride.

146. Why did hatters become mad?

The chemicals used in hat making included mercurous nitrate, which were used to cure felt. Prolonged exposure to the mercury vapors caused mercury poisoning with resultant behavioral changes (e.g., in extreme cases, delirium and personality changes). In Danbury, Connecticut, mercury-induced tremors were called “Danbury shakes.” Mad hatter disease is sometimes called *erethism*.

147. Why is cyanide so toxic?

Cyanide ion binds to the heme-containing cytochrome as an enzyme in the electron transport chain of mitochondria, which is the final common pathway in oxidative metabolism. Thus, with a significant exposure, virtually every cell in the body becomes starved of oxygen at the mitochondrial level and is unable to function. The body does have minor routes of cyanide detoxification, including excretion by the lungs and liver through rhodanese, a hepatic enzyme that combines cyanide with thiosulfate to form the less toxic thiocyanate for renal excretion. However, these mechanisms are inadequate in the face of a significant cyanide exposure. As with CO poisoning, symptoms tend to be most prominent among the metabolically active organ systems. In particular, the CNS is rapidly affected, causing headache and dizziness, which may progress to prostration, convulsions, coma, and death. Less severe ingestions may be noted initially by burning of the tongue and mucous membranes, with tachypnea and dyspnea due to cyanide stimulation of chemoreceptors.

148. In what settings should cyanide poisoning be suspected?

- **Suicidal ingestion**, often involving chemists who have access to cyanide salts as reagents
- **Fires** causing combustion of materials such as wool, silk, synthetic rubber, polyurethane, and nitrocellulose, resulting in the release of cyanide
- Patients who are on **nitroprusside continuous infusion**, an antihypertensive agent that contains five cyanide moieties per molecule

149. What kinds of plants account for the greatest percentage of deaths due to plant poisonings?

Mushrooms account for at least 50% of deaths due to plant poisoning. The most dreaded variety is the *Amanita* species, which initially causes intestinal symptoms by one toxin (phallotoxin) and then hepatic and renal failure by a separate toxin (amatoxin). Other mushroom classes can cause a variety of early-onset ($<$6 hours) symptoms, including muscarinic effects (e.g., sweating, salivation, colic), anticholinergic effects (e.g., drowsiness, mania, hallucinations), gastroenteritis, and Antabuse-type effects if taken with alcohol.

150. Is mistletoe toxic?

Mistletoe, the popular Christmas plant, is an evergreen with small white berries. Ingestion of small amounts of the berries, leaves, or stems may result in GI symptoms, including pain, nausea, vomiting, and diarrhea. Rarely, large ingestions have resulted in seizures, hypertension, and even cardiac arrest. In some countries, extracts of mistletoe have been used for illegal abortifacients, brewed in teas that are particularly toxic. In the United States, the typical call to a poison center concerns a child who eats one or two mistletoe berries, which in general is unlikely to produce significant signs or symptoms.

151. Should swallowed disc batteries be removed?

Although the concern is that a disc battery may produce corrosive intestinal injury, most traverse the GI tract without incident. An initial radiograph for localization is indicated. If the disc battery is in the esophagus, *emergent* removal is required. Otherwise, if the battery is in the stomach or beyond and the patient remains asymptomatic, watchful waiting may be appropriate with follow-up imaging if the battery is not seen in the stool.

National Poison Control Center. www.poison.org/battery/guideline. Accessed July 30, 2019.

Litovitz T, Whitaker N, Clark L, et al. Emerging battery-ingestion hazard: clinical implications. *Pediatrics.* 2010;125(6):1168–1177.

152. What are the available methods used to remove a foreign body from the esophagus?

Three methods are used; local custom prevails regarding selection.

- **Esophagoscopy**, the most commonly used method, is done under general anesthesia.
- A **Foley catheter** can be inserted beyond the foreign body, inflated, and then pulled back to remove the object. This extraction method is used by various centers, particularly for coins if the ingestion is less than 24 hours old and no respiratory distress is present. Complications, such as airway obstruction by a displaced coin and esophageal perforation, are possible. This can be a dangerous procedure and should only be attempted by those with experience.
- In **bougienage**, the object is forced into the stomach.

153. What recreational drug is most frequently associated with rave parties?

Rave parties are large parties or festivals featuring live performances of electronic dance music, laser light shows, projected images, visual effects, and smoke machines. A number of drugs are associated with these events, including LSD and ketamine, but the drug that is most associated with rave parties is **MDMA** (popularly known as **ecstasy** or **Molly**), a psychoactive drug that has similarities to both the stimulant amphetamine and the hallucinogen mescaline.

154. Why is ecstasy considered so dangerous?

Ecstasy is rarely sold as pure ecstasy and often includes other drugs of which the user may not be aware. Therefore its effects are unpredictable. The pure form (known as Molly for "molecular") can cause tachycardia, dry mouth, teeth grinding, and clenched jaw. Severe adverse reactions to the drug include pronounced hyperthermia, seizures, hypertensive crises, dysrhythmias, metabolic disturbances (specifically hyponatremia), DIC, rhabdomyolysis, acute kidney disease, liver toxicity, and stroke. It has also been known to be fatal in some cases. Care is supportive and usually involves some form of cooling.

155. How is the current U.S. opioid crisis affecting pediatric patients outside of the neonatal period?

- The rate of hospitalization and pediatric intensive care unit (PICU) care for the ingestion of opioids by children is increasing.
- The majority of opioid-related hospitalizations involve adolescents 12 to 17 years of age.
- One-third of hospitalizations are of children $<$6 years of age.

- Almost 20% of children 1 to 5 years of age who ingest opioids ingest methadone, suggesting that these young children are at increased risk for opioid ingestion when parents or family members are being treated with methadone for their opioid addictions.
- Opioid overdose is responsible for >50% of drug-related deaths in young people ages 15 to 24 years.
- It is estimated that for every adolescent or young adult overdose death, there are 119 emergency room visits and 22 treatment admissions.

Kane JM, Colvin JD, Bartlett AH, Hall M. Opioid-related critical care resource use in US children's hospitals. *Pediatrics.* 2018;141(4):e20173335.
Gaither JR, Shabanova V, Leventhal JM. US national trends in pediatric deaths from prescription and illicit opioids, 1999-2016. *JAMA Netw Open.* 2018;1(8):e186558.

156. What is "robotripping"?

Robotripping is the intentional misuse of Robitussin DM, a dextromethorphan product often combined with antihistamines and/or pseudoephedrine, to experience a "high." A toxidrome of psychomotor agitation, hostility, grandiose behavior, hallucinations, and paranoia ("intoxication delirium") can result.

Stanciu CN, Penders TM, Rouse EM. Recreational use of dextromethrophan, "Robotripping"—a brief review. *Am J Addict.* 2016;25(5):374–377.

157. Why are synthetic cannabinoids (SCs) particularly worrisome?

SCs may resemble the properties of marijuana but, in many cases, may contain completely different chemical structures and can be 2 to 100 times more potent than natural marijuana. They are sold under various names, including K2 and/or Spice. Common adverse effects include tachycardia, agitation, nausea, generalized tonic-clonic seizures, and psychiatric problems, such as a first episode of psychosis. Additionally, SC use has been associated with acute kidney injury, acute cerebral ischemia, myocardial infarction, and death. Studies reveal SC use in middle and high school students nationwide, from as early as eighth grade, is as high as 3% of students. Marijuana seems to be a predecessor to and predictor of SC use.

Palamar JJ, Barratt MJ, Coney L, Martins SS. Synthetic cannabinoid use among high school seniors. *Pediatrics.* 2017;140(4):e20171330.
Ford BM, Tai S, Fantegrossi WE, Prather PL. Synthetic pot: Not your grandfather's marijuana. *Trends Pharmacol Sci.* 2017;38(3):257–276.

158. Why is possible parental use of e-cigarettes an important historical question to ask if a 20-month-old presents with drooling, diaphoresis, bradycardia, and hypotension?

This child is likely experiencing **acute nicotine toxicity** secondary to ingestion of the e-liquid or e-juice in the cartridges used to create the e-cigarette vapor. *Vaping* is the term given to inhaling and exhaling an e-cigarette. A major draw to e-cigarettes is the more than 15,000 available e-liquid flavors, such as child-friendly varieties, including fruit, candy, "Belgian waffle," and chocolate. Symptoms of acute nicotine toxicity include fine tremor, nausea, tachycardia, and elevated blood pressure. Severe poisonings generally have a biphasic reaction. Early symptoms occur within the first hour of exposure and are characterized by cholinergic excess (i.e., increased salivation, vomiting, and diaphoresis). Other signs may include cardiac dysrhythmias, seizures, and muscle fasciculations. Late symptoms of severe nicotine poisoning occur 30 minutes to 4 hours after ingestion and include hypotension, bradycardia, lethargy, and respiratory failure secondary to neuromuscular blockade.
An ingestion in a 12-kg, 20-month-old child of as little as one-half of a teaspoon could be fatal. Calls to poison control centers for exposures have increased significantly since 2012.

Govindarajan P, Spiller HA, Casavant MJ, et al. E-cigarette and liquid nicotine exposures among young children. *Pediatrics.* 2018;141(5):e20173361.

KEY POINTS: TOXICOLOGY

1. Ipecac is no longer recommended for poisoning.
2. Activated charcoal is most efficacious if given as early as possible after ingestion, although it may still be beneficial several hours after ingestion.
3. Gastric lavage has unproven efficacy for most ingestions.
4. WBI is indicated for sustained-release or enteric-coated substances.
5. Alkalinization of urine is still considered valuable in the management of acute overdoses of salicylates, phenobarbital, or tricyclic antidepressants.
6. The current U.S. opioid crisis in adults is affecting pediatric patients who have access to their parents' opioid medication.

TRAUMA

159. What are the major signs of a blowout fracture?

Traumatic force to the eye can result in a blowout fracture affecting either the orbital floor or the medial wall (Fig. 5.7). The fracture may result from a sudden increase in intraorbital pressure or from a direct concussive force to the bony walls. Symptoms and signs can include the following:

- Pain and/or diplopia with upward gaze
- Compromised upward gaze on the affected side as a result of entrapment of the inferior rectus muscle
- Enophthalmos (i.e., posterior displacement of the globe of the eye)
- Loss of sensation over the upper lip and gums on the injured side
- Crepitus and tenderness over the inferior orbital ridge

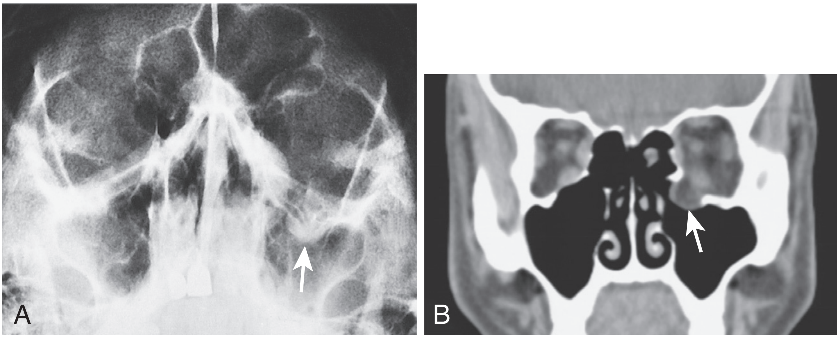

Fig. 5.7 Waters view (A) shows polypoid soft tissue mass in the roof of the left antrum *(arrow)*, which was a blowout fracture of the orbital floor. Coronal CT scan (B) shows the herniated soft tissues *(arrow)* of the blowout fracture. (From Som PM, Curtin HD, ed. *Head and Neck Imaging*. 5th ed. Philadelphia, PA: Mosby; 2011:513.)

160. When evaluating a patient with an eye injury, when should you suspect a ruptured globe, and how should you handle it?

Globe rupture denotes a full-thickness laceration of the cornea and/or sclera. This is an ophthalmologic emergency and must be recognized immediately. The hallmark clinical features include:

- Tear drop pupil
- 360-degree subconjunctival hemorrhage
- Enophthalmos

If globe rupture is suspected, an ophthalmologist should be emergently consulted and the acronym **SANTAS**, should be followed:

- **S**hield should be placed over the eye to protect from further damage.
- **A**ntiemetics should be given to protect against increased pressure.
- **N**PO (nothing per oral, or by mouth) to prepare for surgery.
- **T**etanus shot should be given.
- **A**nalgesics, either parenteral or oral (avoid topical), should be administered.
- **S**edation, if not contraindicated by other injuries, should be given.

Levin A. Eye trauma. In Fleischer GR, Ludwig S, eds. *Textbook of Pediatric Emergency Medicine*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2010:1448–1453.

161. When should an avulsed tooth be reimplanted?

Avulsion is the complete displacement of the tooth from its socket. Primary teeth (i.e., baby teeth) should not be reimplanted because nerve root damage or dental ankylosis may result. Secondary teeth should be repaired as soon as possible to maximize the chance of tooth viability. An avulsed tooth may be stored in cold milk or saline or placed under a cooperative patient's tongue and should be reimplanted as quickly as possible.

Emerich K, Wyszkowski J. Clinical practice: dental trauma. *Eur J Pediatr.* 2010;169(9):1045–1050.

162. What are the three most important considerations when evaluating nasal trauma?

- **Bleeding:** If persistent, bleeding should be controlled with pressure, ice, topical vasoconstrictors, cauterization, and anterior or posterior nasal packing.
- **Septal hematoma:** If the nasal septum is bulging into the nasal cavity, there is likely a hematoma that must be drained. If drainage is not performed, abscess formation or pressure necrosis can result and lead to a saddle-nose deformity.
- **Watery rhinorrhea:** This may be a sign of cribriform plate, suborbital ethmoid, sphenoid sinus, or frontal sinus fracture with cerebrospinal fluid leak.

163. How long can you wait before a broken nose in a child must be reduced?

If a nasal bone fracture causes asymmetry (which is noted as the swelling from acute trauma subsides), the fracture should be reduced **within 4 to 5 days**; a longer delay may result in malunion.

164. After a motor vehicle collision, an 8-year-old presents with right-sided pain, a heart rate of 150 beats per minute, a blood pressure of 110/80 mm Hg, and capillary refill time of 3.5 seconds. How should his initial fluid therapy be managed?

It is important to recognize that this child is in shock, despite a normal blood pressure for age. For children in shock, changes in blood pressure are often late and precipitous. Findings of tachycardia, prolonged capillary refill, and diminished pulses are indicative of *intravascular hypovolemia* in this patient, requiring aggressive fluid resuscitation. Isotonic crystalloid (saline or lactated Ringer solution) should be given in boluses of 20 mL/kg over 5 to 10 minutes. If, after 60 mL/kg of crystalloid, hemodynamic measures have not improved or have worsened, blood products should be given in 10-mL/kg boluses.

165. What are the signs and symptoms of a tension pneumothorax?

A *tension pneumothorax* presents with hypotension, respiratory distress, diminished breath sounds on the affected side, and tracheal deviation. Treatment begins with emergent needle decompression in the second intercostal space at the midclavicular line followed by chest tube placement.

166. Which children with acute minor blunt head trauma require emergency CT scans?

The largest prospective study of children <18 years with head trauma (>42,000 patients) was designed to determine which patients are at very low risk for clinically important traumatic brain injury (ciTBI) for whom CT is unnecessary and clinical observation can suffice. Derived and validated prediction rules were developed based on age. Subsequent implementation has been shown to significantly decrease CT use without any significant increase in missed ciTBI. Negative predictive values (i.e., the likelihood of something not being present, in this case, significant brain injury) were 100% for the younger group and 99.95% for the older group (and thus CT was thought to be unnecessary) if the following were characteristics were seen on evaluation:

- **Younger than 2 years:** Normal mental status, no scalp hematoma except frontal, no loss of consciousness or loss of consciousness for less than 5 seconds, nonsevere injury mechanism (e.g., fall of less than 3 feet, motor vehicle collision without patient ejection or death of another passenger, no head injury by high-impact object), no palpable skull fracture, acting normally according to parents
- **Age 2 years and older:** Normal mental status, no loss of consciousness, no vomiting, nonsevere injury mechanism, no signs of basilar skull fracture, no severe headache

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Puffenbarger MS, Ahmad FA, Argent M, et al. Reduction of computed tomography use for closed head injury evaluation at a nonpediatric community emergency department. *Acad Emerg Med.* 2018;26(7):784–795.

Bregstein JS, Lubell TR, Ruscica AM, Roskind CG. Nuking the radiation: minimizing radiation exposure in the evaluation of pediatric blunt trauma. *Curr Opin Pediatr.* 2014;26(3):272–278.

Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk for clinically important brain injuries after head trauma: a prospective cohort study. *Lancet.* 2009;374(9696):1160–1170.

167. When intracranial pressure is acutely elevated, how long is it before papilledema develops?

Generally, 24 to 48 hours.

168. What are the components of the Glasgow Coma Scale?

Developed in 1974 by the neurosurgical department at the University of Glasgow, the scale was an attempt to standardize the assessment of the depth and duration of impaired consciousness and coma, particularly in the setting of trauma. The scale is based on eye opening, verbal responses, and motor responses, with a total score that ranges from 3 to 15. Higher numbers indicate more increased levels of consciousness. For younger children (<2 years), a pediatric version of the Glasgow Coma Scale was devised for assessment of age-appropriate behavior, particularly in preverbal infants (Table 5.6).

Table 5.6 Glasgow Coma Scale

	GLASGOW COMA SCALE	GLASGOW COMA SCALE, PEDIATRIC VERSION	SCORE
Best Verbal Response	Oriented, appropriate conversation	Age-appropriate vocalization (e.g., smiles, coos, babbles, follows object)	5
	Disoriented, confused conversation	Irritable crying	4
	Inappropriate words	Cries to pain	3
	Incomprehensible sounds	Moans to pain	2
	No response	No response	1
Best Motor Response	Obeys a verbal command	Moves spontaneously and purposefully	6
	Localizes pain	Withdraws to touch	5
	Withdraws to pain	Withdraws to response in pain	4
	Abnormal flexion (decorticate posturing)	Abnormal flexion	3
	Abnormal extension (decerebrate posturing)	Abnormal extension	2
	No response	No response	1
Eye Opening	Spontaneous	Spontaneous	4
	To speech or sound	To speech or sound	3
	To pain only	To pain only	2
	No response	No response	1

169. How does the location of cervical spine fractures vary between younger children and older children and adults?

Younger children tend to have fractures of the upper cervical spine, whereas older children and adults have fractures more often involving the lower cervical spine, for the following reasons:

- Changing fulcrum of the spine: In an infant, the fulcrum of the cervical spine is at approximately C2–C3; in a child who is 5 to 6 years old, the fulcrum is at C3–C4; from 8 to adulthood, it is at C5–C6. These changes are in large part the result of the relatively large head size of a child compared with that of an adult.
- Younger children have relatively weak neck muscles.
- Younger children have poorer protective reflexes.

Woodward GA. Neck trauma. In Fleisher GR, Ludwig S, eds. *Textbook of Pediatric Emergency Medicine*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2010;1379–1380.

170. What is SCIWORA?

SCIWORA stands for **S**pinal **C**ord **I**njury **W**ithout **R**adiographic **A**bnormality. SCIWORA is most commonly seen in children <8 years of age. These patients have signs and symptoms that are consistent with spinal cord injury, but radiographic and CT studies reveal no bony abnormalities. It is postulated that the highly malleable pediatric spine allows the cord to sustain injury from flexion-extension forces without causing bony disruption. MRI often reveals spinal cord injury in these cases. The initial neurologic complaints of these children should be taken seriously. Even with normal radiographs, a patient with an altered sensorium or with neurologic abnormalities that are consistent with cervical cord injury (e.g., motor or sensory changes, bowel and bladder problems, vital sign instability) requires continued neck immobilization and more extensive evaluation.

171. Are single lateral cervical spine radiographs sufficient to “clear” a patient after neck injury?

No. In some studies, the sensitivity of a single view for fractures is only 80%. The American College of Radiology guidelines recommend at least three views: (1) anteroposterior (including the C7–T1 junction, C1–C7), (2) lateral, and (3) open mouth (odontoid). The last view is often difficult to obtain in younger children. CT and MRI are reserved for more extensive evaluation for spinal cord injury when the initial three views are negative in symptomatic patients. The use of oblique films is controversial.

Booth TN. Cervical spine evaluation in pediatric trauma. *Am J Roentgenol.* 2012;198(5):W217–225.
Eubanks JD, Gilmore A, Bess S, et al. Clearing the pediatric cervical spine following injury. *J Am Acad Orthop Surg.* 2006;14:552–564.

172. If the abdominal CT scan is negative in a patient with blunt abdominal trauma, can you be certain that there is no intra-abdominal injury?

No. CT scans may miss some bowel, diaphragmatic, and pancreatic injuries. If the CT shows free fluid in the abdominal cavity but no obvious organ injury, there may be injury to the GI tract or the mesentery. Worsening abdominal pain or persistent emesis requires serial examinations, possible repeat CT scan, and, at the discretion of the surgeon, exploratory laparotomy.

Wegner S, Colletti JE, Van Wie D. Pediatric blunt abdominal trauma. *Pediatr Clin North Am.* 2006;53(2):243–256.

173. Why is left shoulder pain after abdominal trauma a worrisome sign?

This may represent blood accumulating under the diaphragm, resulting in pain referred to the left shoulder *(Kehr sign)*. The sign can be elicited by left upper quadrant palpation or by placing the patient in the Trendelenburg position. The finding is worrisome because it suggests possible solid organ abdominal injury—most commonly splenic injury—and requires surgical consultation and radiographic studies (ultrasound and CT scan) to grade the extent of injury.

Powell M, Courcoulas A, Gardner M, et al. Management of blunt splenic trauma: significant differences between adults and children. *Surgery.* 1997;122(4):654–660.

174. A 5-year-old child has ecchymosis of the lower abdomen after a motor vehicle collision. What should you immediately suspect?

This child's injuries should immediately key you in to the possibility of a **lap-belt injury**. In children who are either too young ($<$8 years old) or too small, the lap belt of a car rests abnormally high on the child's body and, instead of crossing the lap at the hips, crosses the lap at the lower abdomen. The most common injuries to suspect are lumbar spine injuries, particularly a flexion disruption (Chance) fracture and bowel or bladder perforations or injury.

Sivit CJ, Taylor GA, Newman KD, et al. Safety-belt injuries in children with lap-belt ecchymosis: CT findings in 61 patients. *Am J Radiol.* 1991;157(1):111–114.

175. In a 7-year-old boy with a radiographically proven pelvic fracture, what diagnostic procedure should be done?

The urethra, as it passes through the prostate, is very close to the pubic bone and is thus susceptible to injury from a pelvic fracture. Urethral damage should be suspected in all patients with pelvic fractures, even those without hematuria. The recommended diagnostic procedure is a **retrograde urethrogram**. It is always important to do a gastrourinary (GU) examination on all trauma patients.

176. Why is catheterization contraindicated if there is blood at the tip of the penis in a child with a pelvic fracture?

A boggy, high-riding prostate found on rectal examination and blood seen at the urethral meatus are clinical signs of **possible urethral disruption**; these two findings are contraindications for passing a Foley catheter. A partial urethral disruption could potentially be made into a complete one with the passing of the catheter.

177. What is POCUS?

***P**oint-**o**f-**c**are **u**ltra**s**onography (POCUS)* is the utilization of bedside ultrasound to guide procedures and aid in timely and accurate diagnoses in the pediatric ED. POCUS is growing in its use for clinical decision-making and for guidance to the need for more comprehensive diagnostic imaging for patients.

178. In what clinical scenarios can POCUS studies be utilized?

- **Trauma:** abdominal or pericardial bleeding secondary to trauma (FAST examination; see question 179)
- **Cardiac/inferior vena cava (IVC):** pericardial effusion, global cardiac function, IVC to assess volume status
- **Lung:** pneumonia, pleural effusion, pneumothorax
- **Abdomen:** appendicitis, pyloric stenosis, intussusception, biliary tract, bladder volume
- **Soft tissue:** cellulitis vs. abscess, lymphadenitis, detection of foreign bodies
- **Female pelvis:** transvaginal/transabdominal ultrasound to look for an intrauterine pregnancy
- **Musculoskeletal:** joint effusion, fractures
- **Procedure guidance:** abscess drainage, vascular access, lumbar puncture, nerve blocks

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Marin JR, Abo AM, Arroyo AC, et al. Pediatric emergency medicine point-of-care ultrasound: summary of the evidence. *Crit Ultrasound J.* 2016;8(1):16.

179. What is the focus of the FAST examination?

FAST stands for **F**ocused **A**ssessment with **S**onography in **T**rauma. It is used as a screen for abdominal and pericardial bleeding, as blood appears black (hypoechoic) against the bright (hyperechoic) background of the internal organs. A FAST examination evaluates four principal areas for bleeding: the *pericardial sac,* the *hepato-renal fossa* (Morrison pouch), the *spleno-renal fossa*, and the *pelvis* (pouch of Douglas). This noninvasive tool provides clinicians with rapid information about potentially life-threatening thoracic and abdominal injury. In victims of blunt abdominal trauma who are unstable, a positive FAST examination may be an indication that the patient needs urgent surgical intervention.

Marin JR, Abo AM, Arroyo AC, et al. Pediatric emergency medicine point-of-care ultrasound: summary of the evidence. *Crit Ultrasound J.* 2016;8(1):16.

180. In children with blunt thoracic trauma, what clinical examination findings predict a low risk for significant injury?

A prospective clinical prediction rule identified the following clinical predictors for very low risk for thoracic injury in children with good sensitivity:

- Normal systolic blood pressure
- Normal respiratory rate
- Normal thoracic examination
- Normal chest auscultation
- No femur fracture
- Glasgow Coma Scale score of 15

Holmes JF, Sokolove PE, Brant WE, et al. A clinical decision rule for identifying children with thoracic injuries after blunt torso trauma. *Ann Emerg Med.* 2022;39(5):492–499.

181. In children with blunt abdominal trauma, are there clinical findings that predict low risk for clinically important injury?

The PECARN (Pediatric Emergency Care Applied Research Network) group prospectively enrolled 12,000 children after blunt abdominal trauma. If the following predictors were present, the rule correctly identified 99% of the children as low risk:

- No evidence of abdominal wall trauma or seat-belt sign
- Glasgow Coma Scale score >13
- No abdominal tenderness
- No evidence of thoracic wall trauma
- No complaints of abdominal pain
- No decreased breath sounds
- No vomiting

Holmes JF, Lillis K, Monroe D, et al. Identifying children at very low risk of clinically important blunt abdominal injuries. *Ann Emerg Med.* 2013;62(2):107–116.

WOUND REPAIR

182. What advice should be given over the telephone regarding the transportation of an avulsed digit?

Wrap the severed piece in dry gauze (sterile, if possible). Place the wrapped piece in a small, sealed plastic bag to minimize its contact with water. Place this bag in a container filled with ice. It is incorrect to place the avulsed piece in any liquid because this causes tissue swelling. Direct contact with ice is to be avoided to prevent tissue necrosis.

183. Which lacerations should be referred to a surgeon or an ED physician who is familiar with wound repair?

- Large, complex lacerations
- Stellate or flap lacerations
- Lacerations with questions of tissue viability
- Lacerations involving lip margins (vermilion border)
- Deep lacerations with nerve or tendon damage
- Knife and gunshot wounds
- Strong concern about cosmetic outcome by either the patient or the family
- Lacerations involving open fractures or joint penetration
- Lacerations involving the inner eyelid, due to the potential of damage to the tear ducts
- Deep lacerations involving the cheek, due to potential damage to the parotid or facial nerve

184. How many days should sutures remain in place?

Blood supply dictates healing; the more blood, the better and the faster the healing.

- *Eyelids*—3 days
- *Face, scalp*—5 days
- *Trunk, upper extremities*—7 to 10 days
- *Lower extremities*—8 to 10 days

185. When should a nerve injury be suspected in a finger laceration?

- **Abnormal testing of sensation** (diminished pain or two-point discrimination)
- **Abnormal autonomic function** (absence of sweat or lack of skin wrinkling after soaking in water)
- **Diminished range of motion of finger** (may also indicate joint, bone, or tendon disruption)
- **Pulsating blood emerging from the wound** (on the flexor aspect, the nerve is superficial to the digital artery, and arterial flow implies nerve damage)

186. What should be done if nerve damage is suspected?

For injuries to major nerves (e.g., the brachial plexus), immediate consultation is necessary. If the digital nerve is injured, immediate repair is not essential, and this is not a true emergency. Delayed nerve repair is very satisfactory, particularly in younger children. If an operating suite and personnel are not poised to proceed, skin closure can be done and the operation deferred (after surgical consultation). Care must be taken to avoid the use of a hemostat or clamp to stop arterial bleeding because this may cause further damage to the nerve. Simple pressure—often for extended periods—generally suffices.

187. Which lacerations should not be sutured?

Lacerations at high risk for infection should be considered for healing by secondary intention or delayed primary closure. As a general rule, these include cosmetically unimportant puncture wounds, human bites, lacerations involving mucosal surfaces (e.g., mouth, vagina), and wounds with a high probability of contamination (e.g., acquired in a garbage bin). Many authorities in the past recommended that wounds untreated for more than 6 to 12 hours on the arms and legs and for 12 to 24 hours on the face not be sutured. However, the type of wound and risk for infection are more important than any absolute time criterion. For example, a clean laceration of the face should be considered for suturing even 24 hours after the injury. A good rule of thumb is as follows: If you can irrigate and clean a wound to the point at which it looks “fresh,” you are safe to close it primarily. Otherwise, you should let it heal by secondary intention.

KEY POINTS: LACERATIONS

1. The best defense against infection in the setting of wound closure is copious irrigation.
2. Irrigation can be painful and should be done *after* local anesthetic is applied or infiltrated.
3. Irrigation can be done with a number of different fluids, including sterile water, normal saline, or tap water, but should not be done with betadine-containing fluids, which are abrasive to the tissue.
4. There is no one universal suture material that is good for all wounds. The material should be chosen based on location, size, and depth of the wound and the tensile strength that is required to easily oppose the wound edges.
5. Suspect digital nerve injury if there is abnormal sensation, abnormal autonomic function, diminished range of motion of the finger, or pulsating blood emerging from the wound.

188. Which are at greater risk for infection, dog bites or cat bites?

Generally, infection rates are higher in **cat bites** because of the greater likelihood of a puncture wound rather than a laceration injury. Additionally, *Pasteurella multocida,* which is the most common pathogen responsible for infection, is present in higher concentrations in cat bites. Wounds caused by cat and dog bites usually contain multiple other organisms, including *Staphylococcus aureus*; *Moraxella*, *Streptococcus*, and *Neisseria* species; and anaerobes.

Ellis R, Ellis C. Dog and cat bites. *Am Fam Physician.* 2014;90(4):239–243.
Talon DA, Citron DM, Abrahamian FM, et al. Bacteriologic analysis of infected dog and cat bites. *N Engl J Med.* 1999;340:85–92.

189. Should antibiotic prophylaxis be given for dog, cat, and human bites?

This is a controversial topic. Although antibiotics are widely prescribed following bites, prophylactic antibiotics have been shown to significantly reduce infections in only two settings: bites to the hands and human bites. Some experts recommend treatment for other “high-risk” injuries such as cat bites, foot wounds, puncture wounds, wounds in immunocompromised patients, and wounds treated initially after 12 hours. It is important that all such wounds first be irrigated, cleaned, and débrided as necessary.

Edens MA, Michel JA, Jones N. Mammalian bites in the emergency department: recommendations for wound closure, antibiotics, and postexposure prophylaxis. *Emerg Med Pract.* 2016;18(4):1–20.
Singer AJ, Dagum AB. Current management of acute cutaneous wounds. *N Engl J Med.* 2008;359(10):1037–1046.

190. Which animals most often carry the rabies virus?

Although all species of animals are susceptible to rabies virus infection, only a few species are important as reservoirs for the disease. Before 1960, the majority of cases of rabies involved domestic animals. Now more than 90% of all animal cases reported to the Centers for Disease Control and Prevention (CDC) occur in wildlife. In the United States, rabies has been identified most commonly in **raccoons, skunks, bats, foxes,** and **coyotes.**

CDC. Rabies Domestic Animal. www.cdc.gov/rabies/exposure/animals/index.html. Accessed June 6, 2019.

191. Which are more likely to be rabid: cats or dogs?

During 2015, more **cats** than dogs were reported rabid in the United States. This may be due to the facts that there are fewer cat vaccination laws, fewer leash laws with cats, and cats tend to roam more freely than dogs. Rabies, however, is uncommon in both. Only 0.3% (244 cats, 67 dogs) of all cats and dogs tested in 2015 were positive for rabies.

CDC. Rabies Domestic Animals. www.cdc.gov/rabies/exposure/animals/domestic.html. Accessed June 6, 2019.

192. If at a local petting zoo a playful 20-month-old child is bitten by a duck, scratched by a rabbit (breaking skin), spit on by a camel, and licked on the face by a horse, should rabies prophylaxis be given?

In general, no prophylaxis is needed for any of these animal wounds unless the animal is actively rabid. The local health department should be contacted if there is any question. Immediate rabies vaccination and rabies immune globulin are recommended for bites or scratches from bats, skunks, raccoons, foxes, and most other carnivores if these injuries break the skin. Bites from dogs and cats generally do not necessitate prophylaxis if the animal is healthy and can be observed closely for a 10-day period. No case in the United States has been attributed to a dog or cat that has remained healthy for the confinement period of 10 days.

American Academy of Pediatrics. Rabies. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *2018 Red Book*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:673–676.

193. When is the use of lidocaine with epinephrine contraindicated as a local anesthetic?

Lidocaine with epinephrine is contraindicated when there is a question of tissue viability and in any instance in which vasoconstriction might produce ischemic injury to an end organ without an alternative blood supply (e.g., tip of the nose, margin of the ear, tip of the finger or toe).

194. What are methods for decreasing the pain of local lidocaine infiltration?

- Infiltration into the subcutaneous layer
- Infiltration at a slow rate
- Buffering the anesthetic (e.g., with bicarbonate; there is no magic formula, but one that works is 10 parts lidocaine and 1 part bicarbonate)
- Warming the anesthetic to body temperature
- Using a small-gauge needle (e.g., 30 gauge)
- Distraction techniques

195. What are some of the ingredients in the alphabet soup of topical anesthetics?

- **LET** (4% **l**idocaine, 0.1% **e**pinephrine, and 0.5% **t**etracaine)
- **TAC** (**t**etracaine, **a**drenaline, and **c**ocaine)
- **LMX** (4% and 5% **l**idocaine gel)
- **V-TAC** (**v**iscous TAC)
- **PLP** (**p**rilocaine, **l**idocaine, and **p**henylephrine)
- **EMLA** (**e**utectic **m**ixture of **l**ocal **a**nesthetics, typically lidocaine and prilocaine)

TAC was among the first of these to be developed, but its higher costs and safety concerns (as a result of the cocaine component) have resulted in others, particularly LET, replacing it as first-line therapy. The AAP recommends the use of topical anesthetics, such as LET, for simple lacerations of the head, neck, and extremities or trunk <5 cm in length. Systemic toxicity can occur through excessive absorption of topical anesthetics; however, this can be minimized by avoiding mucosal membranes and large open wounds.

Zempsky WT. Pharmacologic approaches for reducing venous access pain in children. *Pediatrics.* 2008;122(Suppl 3):S140–S153.

196. When should tissue adhesives be considered or avoided?

***Consider* tissue adhesives for the following:**

- Wounds with good edge approximation and little wound tension
- Wounds that are clean and linear
- Wounds that ordinarily, if sutured, would require sutures 5-0 or smaller (i.e., wounds with little tension)

***Avoid* tissue adhesives for the following:**

- Wounds where good edge approximation cannot be achieved (e.g., jagged wounds)
- Bite or puncture wounds
- Generally, wounds deeper than 5 mm
- Hands, feet, or joints, unless the affected area can be immobilized
- Oral mucosa or other mucosal surfaces, or areas with increased amounts of moisture as in the perineum or axilla
- Patients with conditions that may delay wound healing (e.g., diabetes mellitus or patients on long-term steroids)

197. In which situations might you choose absorbable over nonabsorbable sutures when repairing a pediatric laceration?

An absorbable suture is generally one that loses most of its tensile strength in 1 to 3 weeks and is fully absorbed within 3 months. Traditionally, absorbable sutures were used only for deep sutures. However, recently, the use of absorbable sutures for percutaneous closure of wounds in adults and children has been advocated. The advantages of absorbable sutures include the elimination of a follow-up visit to remove the patient's sutures and the possibility of decreased scarring and infection. Ideal wound candidates for absorbable sutures include the following:

- **Facial lacerations**, where skin heals quickly and prolonged intact sutures may lead to a suboptimal cosmetic result. (Fast-absorbing sutures, which become absorbed in less than 1 week, are particularly good on facial wounds.)
- Percutaneous closure of **lacerations under casts or splints**.
- Closure of **lacerations of the tongue or oral mucosa**.
- **Hand and finger lacerations**.
- **Nail bed lacerations**.

198. How do you choose your suture size?

The choice of suture size is based on multiple factors, such as skin tension, depth of wound, and exact location of laceration. However, in general, the following guidelines can be used:

- **3-0** for most deep sutures on the trunk and limbs
- **4-0** for deep sutures and in injuries in non–weight-bearing areas
- **5-0** for most facial or other superficial repairs
- **6-0** for some facial repairs and only if there is no wound tension

199. What is the proper fluid to use for wound irrigation?

Normal saline, sterile water, or even tap water may be used. The key appears to be the flushing action, rather than the fluid. Some authors argue that for a number of reasons—availability, low cost, efficiency, and effectiveness—tap water should be strongly considered for wound cleansing in the ED. Other cleansing solutions and antiseptics, such as betadine and alcohol, remain controversial because of toxic effects on tissue and lack of significant clinical benefit.

Cooper DD, Seupaul RA. Is water effective for wound cleansing? *Ann Emerg Med.* 2012;60(5):626–627.

200. How is conscious sedation best managed in children?

There is no single best method for the conscious sedation of pediatric patients for diagnostic, radiologic, or minor surgical procedures. Surveys indicate that a wide variety of approaches are used in emergency rooms and radiology suites, including opioids (morphine, fentanyl), benzodiazepines (diazepam, midazolam), barbiturates (pentobarbital, thiopental), and nonbarbiturate anesthetic-analgesic agents (ketamine). Although conscious sedation, by definition, is a state of medically controlled depressed consciousness with a patent airway, maintained protective reflexes, and appropriate responses to stimulation on verbal command, the potential for rapidly developing problems should be anticipated. These can include hypoventilation, apnea, airway obstruction, and cardiorespiratory collapse. Consequently, pharmacologic agents used for conscious sedation should be administered under supervised conditions and in the presence of competent personnel who are capable of resuscitation, ongoing monitoring (especially pulse oximetry), and sufficient equipment for resuscitation (e.g., positive-pressure oxygen delivery system, suction apparatus). As a rule, few office settings are appropriate for conscious sedation.

Jain S. Sedation: a primer for pediatricians. *Pediatr Ann.* 2018;47(6):e254–e258.
Sury M. Conscious sedation in children. *Contin Educ Anaesth Crit Care Pain.* 2012;12:152–156.
Mandt MJ, Roback MG. Assessment and monitoring of pediatric procedural sedation. *Clin Pediatr Emerg Med.* 2007;8:223–231.

201. What are the benefits to using the intranasal route for delivery of pain or sedation medications to children undergoing procedures?

- No intravenous access is needed.
- High vascularization of the nasal mucosa means medications will be absorbed quickly and available sooner with a quick onset of action.
- Well tolerated

202. Which procedural medications can be delivered to children via the intranasal route?

- **Midazolam** will provide anxiolysis but no analgesia. It has been shown to irritate the nasal mucosa as it is administered. Studies have shown good results with premedication with intranasal lidocaine that seems to dull the burning. The medication can be dripped in or administered with an atomizer. Doses ranging from 0.2 mg/kg to 0.5 mg/kg with a maximum of 10 mg have been shown to be effective in patients >6 months of age.
- **Fentanyl** will provide analgesia in doses of 1 to 2 micrograms/kg. Onset of action is 10 to 15 minutes. Adverse effects are rare and include epistaxis, an unpleasant taste, and nasal irritation.
- **Ketamine** is a potent analgesic and sedative, but precise intranasal dosing in the pediatric age group is still being studied.

Del Pizzo J, Callahan J. Intranasal medications in pediatric emergency medicine. *Pediatr Emerg Care.* 2014;30(7):496–501.

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ENDOCRINOLOGY

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CHAPTER 6

ADRENAL DISORDERS

1. What are the symptoms of adrenal insufficiency?

- *Newborns:* Nonspecific findings of vomiting, irritability, and poor weight gain; may progress to cardiovascular shock
- *Children:* Lethargy, easy fatigability, poor weight gain, and vague abdominal complaints; hyperpigmentation (primary insufficiency); symptoms of hypoglycemia (primary or secondary insufficiency); may also exhibit vascular collapse with intercurrent illness

2. What distinguishes primary and secondary adrenal insufficiency?

- *Primary:* Abnormality of the adrenal gland, low cortisol concentration accompanied by an elevated adrenocorticotropic hormone (ACTH) level; may also have mineralocorticoid deficiency
- *Secondary:* Hypothalamic or pituitary dysfunction, low cortisol concentration accompanied by an inappropriately normal or low ACTH level; normal mineralocorticoid production; often associated with multiple pituitary deficiencies

3. What is the differential diagnosis of primary adrenal insufficiency?

- **Inherited enzymatic defects:** congenital adrenal hyperplasia (multiple enzymatic defects are known), congenital adrenal hypoplasia
- **Autoimmune disease:** isolated, autoimmune polyendocrinopathy syndrome (APS) types 1 and 2; type 2 is also known as *Schmidt syndrome*
- **Infectious disease:** tuberculosis, meningococcemia, disseminated fungal infections
- **Trauma:** bilateral adrenal hemorrhage (hemorrhage is common, but adrenal insufficiency is rare)
- **Adrenal hypoplasia:** due to inherited defects in the adrenal ACTH receptors
- **Iatrogenic:** use of exogenous steroids

4. What is the most common form of congenital adrenal hyperplasia (CAH)?

CAH refers to a group of autosomal recessive disorders that results from various enzymatic defects in the biosynthesis of cortisol. Depending on the enzyme involved, the blockade can result in deficiencies and/or excesses in the other steroid pathways (i.e., mineralocorticoids and androgens). **21-hydroxylase deficiency** accounts for more than 90% of cases; the complete (salt-losing, about two-thirds of cases) and partial (simple virilizing) forms occur in about 1 in 12,000 births and have an equal sex distribution. There are substantial differences in prevalence in various racial and ethnic groups. A late-onset or nonclassic attenuated form (mild deficiency) manifests in adolescent girls with hirsutism and menstrual irregularities.

El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. *Lancet.* 2017;11;390(10108):2194–2210.
Zoltan A, Zhou P. Congenital adrenal hyperplasia: diagnosis, evaluation, management. *Pediatr Rev.* 2009;30:e49–e57.

5. In newborns with CAH, why are girls likely to be diagnosed earlier than boys?

The most common forms of CAH result in excess androgen production in the fetus; the effects of prenatal androgen excess on the development of the clitoris and labia majora can be easily identified in the newborn period. In boys, androgen excess does not cause any clearly abnormal appearance of the external genitalia. CAH should always be considered in the differential diagnosis of disorders of external sexual development, particularly in infants with a 46,XX karyotype.

6. How do physiologic, stress, and pharmacologic doses of hydrocortisone differ?

- *Physiologic*: Careful studies have shown that adrenal glucocorticoid production in the normal individual is about 7 to 8 mg/m^2 per 24 hours. Because 50% to 60% of oral hydrocortisone is absorbed, the recommended oral physiologic replacement is about 12 to 15 mg/m^2 per 24 hours.
- *Stress*: On the basis of studies performed before the development of high-quality radioimmunoassays, the consensus opinion was that production of glucocorticoid increased about three fold when individuals were physiologically stressed. Hence, when the term *stress dose* is used, it generally means that the dose is at least three times above physiologic replacement, that is, 50 to 100 mg/m^2 per 24 hours of hydrocortisone.
- *Pharmacologic*: Glucocorticoids are extensively used in pharmacologic doses for the treatment of various inflammatory processes and in surgery or trauma to reduce or prevent swelling and inflammation. Doses of glucocorticoid higher than 50 mg/m^2 per 24 hours of hydrocortisone that are being used to treat these conditions are referred to as *pharmacologic doses*; that is, the medication is not being used for adrenal replacement or stress dosing.

7. When does adrenal–pituitary axis suppression occur in prolonged glucocorticoid treatment?

As a general rule, the longer the duration of treatment and the higher the dose of glucocorticoid, the greater the risk for adrenal suppression. If pharmacologic doses of glucocorticoids are used for less than 10 days, there is a relatively low risk for permanent adrenal insufficiency, whereas daily use for more than 30 days carries a high risk for prolonged or, rarely, permanent adrenal suppression. The reason for glucocorticoid treatment must also be considered; that is, a child with severe head trauma may have initially been on treatment with glucocorticoids to reduce brain swelling but is also at significant risk for secondary pituitary deficiencies.

8. A 4-year-old boy presents to your office for recent onset of body odor. On examination, he is noted to have Tanner II pubic hair. What are the causes of early hair and odor?

Premature pubarche is defined by the early onset of pubic hair, axillary hair, or body odor in girls <8 years and boys <9 years. The differential includes **premature adrenarche** (early signs accompanied by rise in adrenal hormone levels such as dehydroepiandrosterone [DHEAS]), **precocious puberty** (accompanied by testicular enlargement), **CAH**, **adrenal tumor**, or **exogenous steroid/androgen exposure**.

9. What are common symptoms of pheochromocytoma in children?

Pheochromocotyoma is a neuroendocrine tumor arising from the chromaffin cells of the adrenal medulla and/or sympathetic chain that secrete catecholamines. This tumor is rare in children and often associated with familial syndromes such as von Hippel-Lindau, multiple endocrine neoplasia (MEN IIA or IIB), or neurofibromatosis and may be inherited as an autosomal dominant trait. Children often present with **sustained hypertension** (60% to 90%) versus paroxysmal hypertension in adults. Other signs and symptoms include **headache**, **sweating**, **pallor**, **anxiety**, and **nausea**.

Mercado-Asis LB, Wolf KI, Jochmanova I, Taieb D. Pheochromocytoma: a genetic and diagnostic update. *Endocr Pract.* 2018;24(1):78–90.

10. How is pheochromocytoma diagnosed?

The gold standard is to measure **fractionated metanephrine levels** in the urine or plasma. Expected levels more consistent with this tumor are at least three to more than four times the upper limit of the normal reference range. Medications that may interfere with testing include labetalol, levodopa, acetaminophen, tricyclic antidepressants, phenoxybenzamine, calcium channel blockers, and some stimulants (such as caffeine). Imaging studies to confirm the presence of pheochromocytoma can include ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), or metaiodobenzylguanidine (MIBG) scan.

Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma, *J Clin Endocrinol Metab.* 2010;95(5):2023–2037.

11. How does cortisol excess manifest in growth measurements?

In children with exogenous obesity, linear growth is typically enhanced. In children with either endogenous or exogenous hypercortisolism (Cushing syndrome), significant obesity can occur in the absence of adequate height growth.

12. How do the major steroid preparations vary in potency?

See Table 6.1.

Table 6.1 Potency of Common Steroid Preparations

NAME	RELATIVE GLUCOCORTICOID POTENCY	RELATIVE DOSING (MG)	RELATIVE MINERALOCORTICOID POTENCY
Cortisone	1	100	+
Hydrocortisone	1.25	80	++
Prednisone	5	20	+
Prednisolone	5	20	+
Methylprednisolone	6	16	0
9a-Fluorocortisol	20	5	+++++
Dexamethasone	50	1	0

Adapted from Donohoue PA. The adrenal cortex. In McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB, eds. *Oski's Pediatrics, Principles and Practice.* 3rd ed. Philadelphia, PA: J.B. Lippincott; 1999:1814.

CALCIUM METABOLISM AND DISORDERS

13. What are the causes of hypercalcemia?

Remember the “**H**igh **5-I-S**” mnemonic: **H** (**h**yperparathyroidism) plus the five **I’s** (**i**diopathic, **i**nfantile, **i**nfection, **i**nfiltration, and **i**ngestion) and **S** (**s**keletal disorders).

- ***Hyperparathyroidism:*** familial, isolated; syndromic
- ***Idiopathic:*** Williams syndrome
- ***Infantile:*** subcutaneous fat necrosis; maternal hypoparathyroidism and inadequate transfer of calcium across the placenta
- ***Infection:*** tuberculosis
- ***Infiltrative:*** cancer (primary bone or metatstatic)
- ***Ingestion:*** milk-alkali syndrome (e.g., excessive supplemental calcium and antacids); thiazide diuretics; vitamin A intoxication; vitamin D intoxication
- ***Skeletal disorders:*** hypophosphatasia; immobilization; skeletal dysplasias

14. What are the causes of hypoparathyroidism?

Parathyroid hormone (PTH) is a calcium regulatory hormone released by the parathyroid glands that increases serum calcium by increasing the resorption of Ca^{2+} from bone and by increasing gastrointestinal and urinary absorption of calcium through the increasing synthesis of calcitriol. *Hypoparathyroidism* can result from a developmental defect, from destruction by surgery or an autoimmune process, or from a biosynthetic defect in hormone production. The result can be acute or chronic hypocalcemia. An intact PTH level should be obtained in all children presenting with hypocalcemia. The result should be interpreted in light of the calcium level; that is, is the PTH appropriately elevated for the degree of hypocalcemia?

Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. *Nat Rev Dis Primers.* 2017;3:170555.
Clarke BL, Brown EM, Collins MT, et al. Epidemiology and diagnosis of hypoparathyroidism. *J Clin Endocrinol Metab.* 2016;101(6):2284–2299.

15. In what clinical circumstances should hypoparathyroidism be suspected?

- Manifestations of hypocalcemia (e.g., carpopedal spasm, bronchospasm, tetany, seizures)
- Lenticular cataracts (these can also occur with other causes of long-standing hypocalcemia)
- Changing behaviors, ranging from depression to psychosis
- Mucocutaneous candidiasis (seen in familial form)
- Dry and scaly skin, psoriasis, and patchy alopecia
- Brittle hair and fingernails
- Enamel hypoplasia (if hypocalcemia is present during dental development)

16. What are the main causes of hypocalcemia in children?

- **Nutritional:** Inadequate intake of vitamin D and, in rare instances, severely inadequate intake of calcium and/or excessive intake of phosphate may cause this condition.
- **Renal insufficiency:** This may be the result of the following: (1) increased serum phosphorus from a decreased glomerular filtration rate with depressed serum calcium and secondary hyperparathyroidism or (2) decreased activity of renal α-hydroxylase, which converts 25-hydroxyvitamin D into the biologically active form, 1,25-$(OH)_2$ D.
- **Nephrotic syndrome:** With lowered serum albumin, total calcium levels are reduced. Additionally, intestinal absorption of calcium is decreased, urinary losses of cholecalciferol-binding globulin are increased, and urinary losses of calcium are increased with prednisone therapy (standard treatment for minimal-change nephrotic syndrome). In patients with hypoalbuminemia, there will be a decrease in total calcium but no decrease in ionized calcium. The corrected calcium is estimated by adding 0.8 mg/dL to the total calcium for every 1-mg decrease in the serum albumin below 4 mg/dL.
- **Hypoparathyroidism:** In infants, this may result from a developmental defect during embryogenesis (parathyroid gland aplasia or hypoplasia) and may occur in the context of a syndrome such as DiGeorge syndrome caused by a deletion in chromosome 22q11. In older children, it may occur in the context of autoimmune polyglandular syndrome (type 1) or mitochondrial myopathy syndromes.
- **Pseudohypoparathyroidism:** This is a group of peripheral resistance syndromes in which resistance to PTH results in elevated PTH levels in the setting of normal renal function and subsequent hypocalcemia due to blunted or absent PTH effect in the setting of high serum concentrations of PTH.
- **Disorders of calcium sensor genes:** Activating mutations of the calcium-sensing receptor gene (CaSR) result in calcium being sensed as normal at subphysiologic levels and PTH secretion switched off inappropriately causing hypoparathyroidism.

Shaw NJ. A practical approach to hypocalcemia in children. *Endocr Dev.* 2015;28:84–100.
Moe SM. Disorders involving calcium, phosphorus, and magnesium. *Prim Care.* 2008;35(2):215–237.
Umpaichitra V, Bastian W, Castells S. Hypocalcemia in children: pathogenesis and management. *Clin Pediatr.* 2001;40(6):305–312.

17. What is the most likely diagnosis in a child with hypocalcemia who has abnormally shaped fingers?

Albright hereditary osteodystrophy (AHO), a type of pseudohypoparathyroidism, is characterized by short stature, obesity, developmental delay, and brachydactyly, specifically a shortening of the fourth and fifth metacarpals (Fig. 6.1).

Desai N, Kalra A. Short fourth and fifth metacarpals. *JAMA.* 2012;308(10):1034–1035.

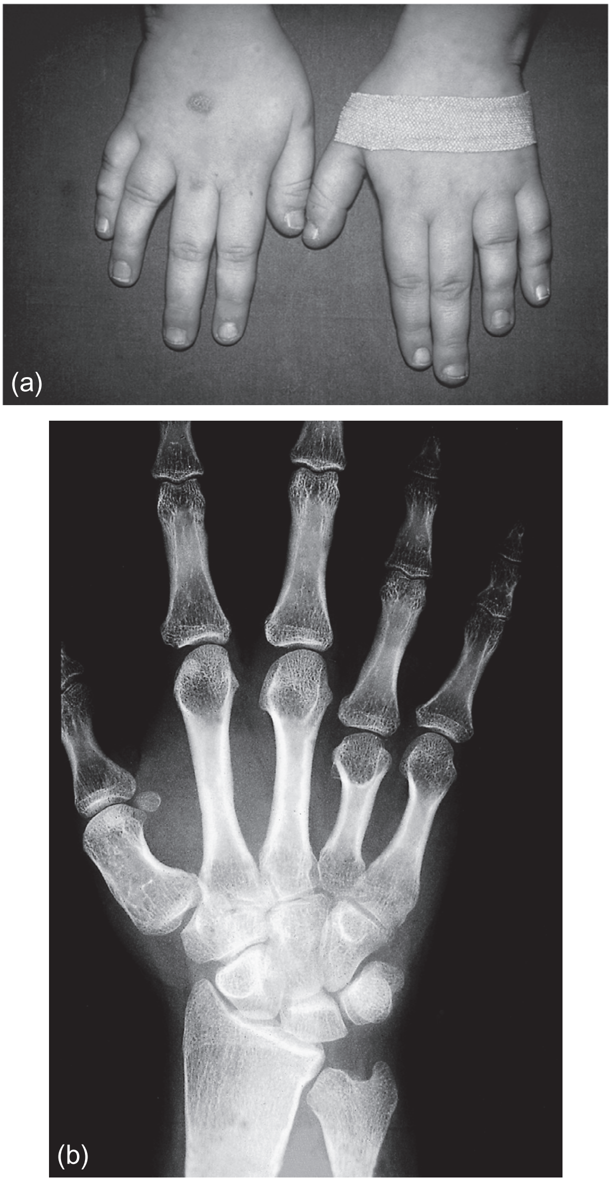

Fig. 6.1 Short fourth and fifth metatarsals of a child (**A**), which are more readily appreciated on the radiograph (**B**). (From Moshang T Jr. *Pediatric Endocrinology: The Requisites in Pediatrics*. Philadelphia, PA: Elsevier Mosby; 2005:8.)

18. What is the difference between rickets and osteomalacia?

Both are due to impaired bone mineralization from one or more factors: vitamin D deficiency, calcium deficiency, or disorders of phosphate or vitamin D metabolism. *Rickets* results in problems with mineralization or bone architecture in growing children when **growth plates are open**. *Osteomalacia* involves the same bony structures, but after **growth plates have fused**.

19. A toddler presents with difficult and delayed walking, bowed legs, and widened wrists. What are other clinical and laboratory features of rickets?

Children may also have frontal bossing and palpable swelling of the costochondral junction (rachitic rosary). Radiologic findings include widening of the growth plate and eventual splaying, cupping, and fraying of the metaphyses, which manifests clinically as an expanded wrist margin (Fig. 6.2). Laboratory evaluation will most commonly reveal low phosphorous, low to normal calcium, low to normal 25-hydroxyvitamin D levels, normal to high PTH, and elevated alkaline phosphatase.

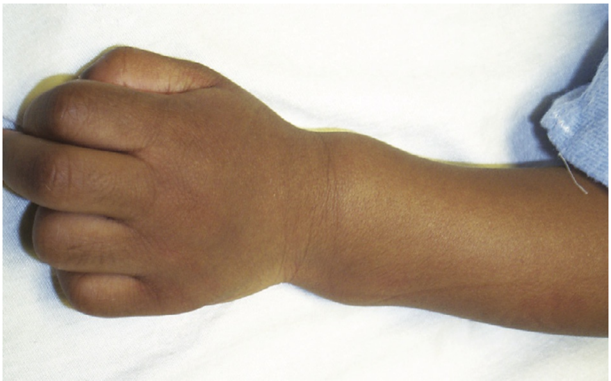

Fig. 6.2 Expansion of the wrist due to underlying metaphyseal widening, a characteristic feature of rickets. (From Zitelli BJ, McIntire SC, Nowalk AJ, eds. *Zitelli and Davis' Atlas of Pediatric Physical Diagnosis*. 7th ed. Philadelphia, PA: Elsevier; 2018:209.)

20. What are two common factors that make vitamin D deficiency such a common problem?

Changes in sun exposure/use of sunscreen and **increases in obesity**. Very few foods naturally contain vitamin D or are fortified with vitamin D. Exceptions are cod liver, tuna, fortified milk, and orange juice. The major source of vitamin D has been exposure to natural sunlight. If an individual wears a sunscreen with a protection factor of 30 or more, vitamin synthesis in the skin is reduced by >95%. If an individual has darker skin, which provides more natural sun protection, he or she requires three to five times longer exposure to make the same amount of vitamin D as a person with a white skin tone. Obesity is also a risk factor, because fat sequesters vitamin D. As sun exposure is reduced because of concerns about potential future malignancies and as obesity rates remain high, vitamin D deficiency is likely to remain a problem.

Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96(7):1911–1930.

21. How much vitamin D should children receive on a daily basis?

Consensus guidelines are that children without risk factors should receive the following amounts of vitamin D at a minimum:

- Infants (<1 year): 400 IU/day
- Children (1 to 18 years): 600 IU/day

All exclusively breastfed infants should receive 400 IU/day of vitamin D supplement because breast milk is low in vitamin D. Some formula-fed infants also require supplementation if their intake is less than approximately 33 ounces of formula daily, which is the quantity needed to receive the recommended amount of vitamin D.

Golden NH, Abrams SA. Optimizing bone health in children and adolescents. *Pediatrics.* 2014;134(4):e1229–e1243.

22. What are the cutoffs for vitamin D deficiency and sufficiency?

The American Association of Pediatrics (AAP) classifies vitamin D status in the pediatric population using the following 25(OH)D concentrations: severe deficiency for values <5 ng/mL; deficiency for values between 5 and 15 ng/mL;

insufficiency for values between 16 and 20 ng/mL; sufficiency for values between 21 and 100 ng/mL; excess for values between 101 and 150 ng/mL; intoxication for values >150 ng/mL.

Antonucci R, Locci C, Clemente MG, et al. Vitamin D deficiency in childhood: old lessons and current challenges. *J Pediatr Endocrinol Metab.* 2018;31(3):247–260.

CLINICAL SYNDROMES

23. A 9-year-old undergoing chemotherapy (including the use of vincristine) is noted to have decreasing urine output and develops a seizure. What electrolyte abnormality is a highly likely cause of his seizure?

Hyponatremia due to SIADH (syndrome of inappropriate secretion of antidiuretic hormone). Antidiuretic hormone (ADH), also known as *vasopressin*, is released from the posterior pituitary gland and serves as a regulator of extracellular fluid volume. The secretion of ADH is regulated by changes in osmolality sensed by the hypothalamus and alterations in blood volume detected by carotid and left atrial stretch receptors. By definition, the secretion of ADH in SIADH is *inappropriate*; therefore the person cannot be given this diagnosis if dehydrated. Medications (including chemotherapeutic agents such as vincristine and cyclophosphamide) can directly promote ADH release and enhance its renal effects. SIADH is usually asymptomatic until symptoms of water intoxication and hyponatremia develop. In this case, a seizure developed. Other symptoms of hyponatremia include nausea, vomiting, irritability, personality changes, and progressive obtundation. An individual with hyponatremia that has developed over a prolonged period is less likely to have symptoms than one in whom the hyponatremia has developed acutely.

Cuesta M, Thompson CJ. The syndrome of inappropriate antidiuresis (SIAD). *Best Pract Res Clin Endocrinol Metab.* 2016;30(2):175–187.

24. What are other causes of SIADH?

- **Intracranial pathology** (increases ADH secretion directly by local central nervous system [CNS] effects): brain tumors, meningitis, encephalitis, stroke, Guillain-Barré syndrome
- **Intrathoracic pathology** (direct stimulation of volume receptors): respiratory failure, pneumonia, tuberculosis, tumors
- **Medications** (either by direct induction of ADH release, by increased sensitivity of vasopressin receptors, by direct agonistic stimulation of renal vasopressin receptor): chlorpropamide, phenothiazine, ifosfamide, carbamazepine, valproic acid, selective serotonin reuptake inhibitors (SSRIs), MDMA (ecstasy)

Shepshelovich D, Schechter A, Calvarysky B, et al. Medication-induced SIADH: distribution and characterization according to medication class. *Br J Clin Pharmacol.* 2017;83(8):1801–1807.

25. What are the five criteria for the diagnosis of SIADH?

1. Hyponatremia with reduced serum osmolality
2. Urine osmolality elevated compared with serum osmolality (a urine osmolality <100 mOsm/dL usually excludes the diagnosis)
3. Urinary sodium concentration excessive for the extent of hyponatremia (usually >20 mEq/L)
4. Normal renal, adrenal, and thyroid function
5. Absence of volume depletion

26. What is cerebral salt wasting (CSW), and how is it separated from SIADH?

CSW is defined as excessive urinary sodium losses in individuals with intracranial disease that result in hyponatremia and dehydration. The mechanism is still not clear. CSW typically develops in the first week after brain injury and generally resolves over time. Both CSW and SIADH are associated with hyponatremia. However, individuals with CSW have signs of intravascular volume depletion (e.g., rapid pulse, low blood pressure), whereas children with SIADH have evidence of intravascular volume overload. In SIADH, fluid restriction often leads to an increase in the serum sodium. In contrast, fluid restriction in CSW will not increase serum sodium but will further impair intravascular volume; therefore it can be dangerous and may result in cardiovascular compromise.

27. What clinical features suggest diabetes insipidus (DI)?

Because DI is caused by an insufficiency of ADH or the inability to respond to ADH, the signs and symptoms tend to be directly related to excessive fluid loss. The clinical spectrum may vary depending on the child's age. The infant may present with symptoms of failure to thrive as a result of chronic dehydration, or there may be a history of repeated episodes of hospitalizations for dehydration. There may also be a history of intermittent low-grade fever.

Often, caretakers report a large volume of intake or an inability to keep a dry diaper on the infant. The higher absorbency of disposable diapers may delay the diagnosis in infants. In the young child, DI may appear as difficulty with toilet training. In the older child, the reappearance of enuresis, increasing frequency of urination, nocturia, or dramatic increases in fluid intake may be noted. Frequent urination with large urinary volumes should lead to the suspicion of DI.

Dabrowski E, Kadakia R, Zimmerman D. Diabetes insipidus in infants and children. *Best Pract Res Clin Endocrinol Metab.* 2016;30(2):317–328.

28. How is the diagnosis of DI made?

Deprivation of water intake for a limited time and judicious monitoring of physical and biochemical parameters may be required. The diagnosis of DI rests on the demonstration of the following: (1) an inappropriately dilute urine in the face of a rising or elevated serum osmolality; (2) urine output that remains high despite the lack of oral input; and (3) changes in physical parameters that are consistent with dehydration (weight loss, tachycardia, loss of skin turgor, dry mucous membranes). A child who, with water deprivation, appropriately concentrates urine ($>$800 mOsm/L) and whose serum osmolality remains constant ($<$290 mOsm/L) is unlikely to have DI. When DI is considered, a pediatric endocrinology consultation is strongly recommended.

If a child meets the criteria for the diagnosis of DI, the water-deprivation test is usually ended with the administration of some form of ADH, such as desmopressin, and the provision of fluids. If the urine subsequently becomes appropriately concentrated, this confirms the diagnosis of ADH deficiency (central DI). Failure to concentrate suggests renal resistance to ADH (nephrogenic DI). DI may often be the first clinical sign of tumor of the hypothalamus or base of the skull (e.g., Wegener granulomatosis, histiocytosis). Brain MRI is recommended if a diagnosis of DI is confirmed.

Kavanagh C, Uy NS. Nephrogenic diabetes insipidus. *Pediatr Clin North Am.* 2019;661(1):227–234.
Ranadive SA, Rosenthal SM. Pediatric disorders of water balance. *Pediatr Clin North Am.* 2011;58(5):1271–1280.

DIABETES

29. What is the pathogenesis of type 1 diabetes mellitus (T1DM)?

T1DM is an autoimmune disease characterized by the destruction of the beta cells in the pancreas. T1DM is a combination of a genetic risk, most strongly associated with genes located in the major histocompatibility complex region on chromosome 6, and a triggering environmental factor that has yet to be elucidated. Mostly newly diagnosed patients do not have a first-degree relative with T1DM; however, a sibling or parent with TIDM increases the risk compared with the general population.

DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet.* 2018;391(10138):2449–2462.
Gregory JM, Moore DJ, Simmons JH. Type 1 diabetes mellitus. *Pediatr Rev.* 2013;34(5):203–215.

30. What are the clinical presentations of T1DM?

T1DM can present with classic symptoms of **polyuria**, **polydipsia** (increased thirst), **polyphagia** (increased hunger), and **weight loss**. There may be additional findings of fatigue, irritability, sore throat, blurry vision, and nocturia. These symptoms may be present for weeks or months before medical attention is sought. New-onset T1DM can also be found incidentally at a well-child checkup. About one-quarter of cases will present with diabetic ketoacidosis (DKA), in which nausea, vomiting, and acidosis have developed. In the most severe cases, there will be altered mental status and Kussmaul respirations (deep and labored breathing). It is important to be vigilant for the symptoms, especially in younger children, in whom polyuria/nocturia is easy to miss if a child is still in diapers.

Klingensmith GJ, Tamborlane W, Wood J, et al. Diabetic ketoacidosis at diabetes onset: still an all too common threat in youth. *J Pediatr.* 2013;162(2):330–334.e1.
Gregory JM, Moore DJ, Simmons JH. Type 1 diabetes mellitus. *Pediatr Rev.* 2013;34(5)203–215.

31. What is the basis of treatment for T1DM?

Care needs to be tailored to the age of the child. The goal is to keep the blood sugar predominantly in the normal range of 80 to 180 mg/dL without excessively low or high blood sugars, both of which are detrimental to the developing child and increase the risk for diabetes complications. The basis of treatment is the **basal bolus insulin** regimen, with a once-daily basal insulin and bolus doses given before meals based on the amount of carbohydrate consumed and the blood sugar. This allows for safety and flexibility in dosing. Patients with type 1 diabetes are best served in a diabetes center with a team approach, including physicians, diabetes educators, nutritionists, social workers, and, if possible, mental health services.

Gregory JM, Moore DJ, Simmons JH. Type 1 diabetes mellitus. *Pediatr Rev.* 2013;34(5)203–215.

32. What is DKA?

DKA is a state of severe metabolic derangement that results from both severe insulin deficiency and increased amounts of counterregulatory hormones (catecholamines, glucagon, cortisol, and growth hormone). The main features are hyperglycemia (glucose >200 mg/dL), ketone production, and acidosis (venous pH <7.30 or serum HCO_3 <15 mEq/L). Patients are generally dehydrated, 5% to 15%, at presentation.

33. What are the mainstays of therapy for DKA?

- Adequate initial supportive care (airway maintenance if necessary, supplemental oxygen as needed)
- Volume resuscitation (which should begin before starting insulin therapy)
- Insulin administration (initial dose of 0.05 to 0.1 unit/kg/hr)
- Frequent monitoring of vital signs, electrolytes, glucose, acid–base status, and mental status

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Olivieri L, Chasm R. Diabetic ketoacidosis in the pediatric emergency department. *Emerg Med Clin North Am.* 2013;31(3):755–773.

34. What should be the initial fluid management in DKA?

The association of the rate of sodium and fluid administration in DKA and the development of cerebral edema remains controversial. The concern is that falling osmolarity might contribute to cerebral edema. The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends the following:

Initial:

- In the rare patient who presents in **shock**, circulatory volume should be rapidly restored with isotonic saline (or lactated Ringer solution) in 20-mL/kg boluses with reassessment after each bolus.
- In patients who are severely volume depleted but not in shock, the initial volume is typically 10 mL/kg given over 1 to 2 hours.

Subsequent:

- Once a patient is hemodynamically stable, fluid replacement is given more slowly. Replacement of the remainder of the fluid deficit (after subtracting the volume of the boluses that were received) is given over the next 48 hours at a rate not to exceed 1.5 to 2 times the maintenance rate. Generally, DKA is associated with an initial weight loss of 7% to 10%.
- Choice of fluid tonicity should be made based on each patient's clinical status (degree of hyperosmolarity, CNS status, serum sodium trend, etc.). ISPAD guidelines state that "no treatment strategy can be definitively recommended as being superior to another based on evidence."

In a 2018 randomized, controlled study involving 13 centers, no difference was found in neurologic outcome of children with DKA with the rate of intravenous (IV) fluid administration or the sodium chloride content (0.9% or 0.45%) of the fluid.

Kupperman N, Ghetti S, Schunk JE, et al. Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. *N Engl J Med.* 2018; 378(24):2275–2287.

Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes.* 2009; 10(Suppl 12):118–133.

35. Why is a falling serum sodium concentration during the treatment of DKA a concern?

Most patients with DKA have a significant sodium deficit of 8 to 10 mEq/kg, which needs to be replaced. After initial fluid boluses, fluids containing 0.5% normal saline or greater are generally required. As a general rule, the serum sodium concentration is low at the outset and rises throughout the course of treatment. An initial sodium concentration of more than 145 mEq/L suggests severe dehydration or hyperosmolarity.

The "corrected" serum sodium should be followed throughout treatment. This value can be calculated using the following equation: Corrected sodium $=$ Measured sodium (mEq/L) $+$ 0.016 $\times$ [serum glucose (mg/dL) - 100]. A corrected serum sodium that begins to fall with treatment merits prompt attention because it indicates either inappropriate fluid management or the onset of SIADH and can signal impending cerebral edema.

Katz MA. Hyperglycemia-induced hyponatremia—calculation of expected serum sodium depression. *N Engl J Med.* 1973; 289(16):843–844.

36. What is the typical potassium status in children with DKA?

In almost all children with DKA, there is a **depletion of intracellular potassium** and a substantial **total body potassium deficit** of 3 to 6 mmol/kg, although the initial measured serum potassium value may be normal or high, in large part because of acidosis. Replacement therapy will be needed. If the patient is hypokalemic, potassium should be given with the initial volume expansion and before insulin administration. Insulin administration results in potassium transport into cells with a further decrease in serum levels. If the initial potassium level is within a normal range, potassium replacement should be initiated (with the concentration in the infusate at 40 mEq/L) after the initial volume expansion and concurrent with starting insulin therapy, provided that urine output can be documented. If the initial potassium measurement is significantly elevated, potassium replacement should be deferred until urine output has been documented and the hyperkalemia abates. Of note, if rapid serum potassium levels are not available, an electrocardiogram (ECG) to look for changes of hypokalemia or hyperkalemia (e.g., T-wave changes) can be valuable in guiding management.

Davis SM, Maddux AB, Alonso GT, et al. Profound hypokalemia associated with severe diabetic ketoacidosis. *Pediatr Diabetes.* 2016; 17(1):61–65.

Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes.* 2009; 10(Suppl 12):118–133.

37. Are there any indications for the use of bicarbonate?

Bicarbonate administration for acidosis in DKA has not been shown to be beneficial in controlled trials. The establishment of an adequate intravascular volume and the provision of sufficient quantities of insulin are far more important in the treatment of DKA than bicarbonate. The decision to initiate bicarbonate therapy should be based on an arterial blood gas level and not a venous blood gas level. Two possible indications include the following:

- **Profound metabolic acidosis** (arterial pH <6.9), which may be compromising cardiac contractility and/or adversely affecting the action of epinephrine during resuscitation
- **Life-threatening hyperkalemia** with bradycardia and severe muscle weakness

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Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes.* 2009; 10(Suppl 12):125.

Green SM, Rothrock SG, Ho JD, et al. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. *Ann Emerg Med.* 1998;31(1):41–48.

38. When should glucose be added to the IV fluids in patients with DKA?

This will depend on the rate at which the serum glucose level is decreasing. Generally, when the glucose level approaches 300 mg/dL, glucose should be added to the IV fluid. It is usually wise to order the appropriate glucose-containing fluid in advance to avoid hypoglycemia. Many centers now use the *“two-bag”* method: they order two bags of IV fluid, with identical electrolyte content except for the glucose concentration. One contains 10% or 12.5% glucose, and the other contains no glucose. As the blood sugar approaches 300 mg/dL, glucose is added to the infusate through a Y tube. With the two-bag system, it is possible to alter the concentration of glucose anywhere between 0% and 12.5%, with a goal of maintaining the blood sugar in the 100- to 200-mg/dL range, thereby avoiding hypoglycemia. It is important to note that if the blood glucose concentration decreases too quickly or is too low before the resolution of acidosis, it is preferable to increase glucose levels by adding glucose to the infusate rather than decreasing the rate of insulin infusion.

Poirier MP, Greer D, Satin-Smith M. A prospective study of the “two-bag system” in diabetic ketoacidosis management. *Clin Pediatr.* 2004;43(9):809–813.

39. Describe the use of insulin in the management of DKA.

Hydration should run for 1 to 2 hours before beginning the insulin drip. Continuous IV insulin infusion should be run at 0.1 u/kg/hr. In small children it can be initiated at 0.05 u/kg/hr. The goal is to drop the glucose at about 50 to 100 mg/dL/hr. *There is NO indication for insulin boluses at the start of therapy.* It is essential to not stop the insulin infusion, as this will only delay the resolution of the acidosis. If needed, more dextrose can be added to the fluid, or the rate of the insulin infusion can be lowered.

Gregory JM, Moore DJ, Simmons JH. Type 1 diabetes mellitus. *Pediatr Rev.* 2013;34(5)203–215.

40. What is the main cause of mortality in DKA?

Cerebral edema. Clinically apparent cerebral edema is rare (occurs in 0.5% to 1% of pediatric cases), but it has been associated with a mortality rate of up to 25% and neurologic impairment in 15% to 30% of cases. Cerebral edema is a clinical diagnosis, not a radiologic one. There can be clinical signs in the absence of radiologic findings, and treatment should never be delayed to obtain a CT.

41. What risk factors are associated with the development of cerebral edema?

The pathogenesis of cerebral edema is incompletely understood. There are likely vasogenic and cytotoxic mechanisms at play. CT studies have demonstrated that *subclinical* cerebral edema may occur in a majority of pediatric patients with DKA. The escalation to life-threatening cerebral edema is unpredictable, often occurring as biochemical abnormalities are improving. It may be sudden in onset or occur gradually, but it typically occurs during the first 5 to 15 hours after therapy begins. It can, however, also occur before treatment. Risk factors identified include the following:

- Younger age
- Newly diagnosed patients
- More profound acidosis
- Attenuated rise in serum sodium during therapy

- Greater hypocapnia (after correcting for acidosis)
- Increased blood urea nitrogen (BUN)
- Bicarbonate therapy for acidosis
- Administration of insulin in first hour of fluid treatment
- Higher volumes of fluid given during the first 4 hours

Agarwal HS. Subclinical cerebral edema in diabetic ketoacidosis in children. *Clin Case Rep.* 2019;7(2):264–267.
Levin DL. Cerebral edema in diabetic ketoacidosis. *Pediatr Crit Care Med.* 2008;9(3):320–329.
Glaser NS, Wootton-Gorges SL, Buonocore MH, et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes.* 2006;7(2):75–80.

42. What signs and symptoms suggest worsening cerebral edema during the treatment of DKA?

- Headache
- Recurrent vomiting
- Change in mental status: increased drowsiness, irritability, restlessness
- Change in neurologic status: cranial nerve palsy, abnormal pupillary responses, abnormal posturing
- Incontinence (age inappropriate)
- Rising blood pressure
- Inappropriate heart rate slowing
- Decreased oxygen saturation

Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes.* 2009; 10(Suppl 12):118–133.

43. How is cerebral edema treated?

If clinical symptoms are present, treatment must be initiated rapidly. **Mannitol** (0.25 to 1.0 g/kg) or **hypertonic (3%) saline** (5 to 10 mL/kg) over 30 minutes can be used under the guidance of an experienced emergency department (ED) or intensive care unit (ICU) attending physician.

Gregory JM, Moore DJ, Simmons JH. Type 1 diabetes mellitus. *Pediatr Rev.* 2013;34(5):203–215.

44. How long does the “honeymoon” period last in patients with newly diagnosed T1DM?

The *honeymoon* usually begins within 2 to 4 weeks after the initiation of insulin treatment. It is a period of decreased exogenous insulin requirements due to residual endogenous insulin production. The honeymoon period may last for a few weeks or months, but it is not predictable. Evidence is accumulating that endogenous insulin production may be preserved by the maintenance of “excellent control” and avoidance of hyperglycemia. Cessation of the honeymoon is often heralded by increasing insulin requirements. This is generally gradual but may be more acute, occurring with an intercurrent illness that increases insulin requirements.

45. What are the pharmacokinetics of various insulin types?

See Table 6.2.

Table 6.2 Pharmacokinetic Properties of Insulin Preparations

PREPARATION	ONSET (HR)	PEAK (HR)	DURATION (HR)
Rapid-Acting			
Regular	0.5-1	2-4	6-8
Lispro	0.25	1	3-4
Aspart	0.25	1	3-4
Glulisine	0.25	1	3-4
Intermediate-Acting			
NPH	1-3	6-8	12-16
Long-Acting			
Glargine U-100	1	NA	29
Glargine U-300*	1	12-16	32-34
Detemir*	1	3-9	6-24

From Atkinson MA. Type 1 diabetes mellitus. In Melmed S, Polonsky K, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology.* 13th ed. Philadelphia, PA: Elsevier; 2016:1469.
NPH, Neutral Protamine Hagedorn.
*May be 20% to 30% less potent than glargine, requiring a higher dose to achieve similar efficacy.

46. What is the basal-bolus method of diabetes management?

The *basal-bolus method* involves the injection of once-daily (sometimes twice-daily) longer-acting insulin *(basal)* to maintain stable blood sugars during times of fasting and separate injections of shorter-acting forms of insulin *(bolus)* before meals and snacks with the dose based on the current blood sugar and carbohydrate content of the food and drink. Basal-bolus regimens are designed to try to match the body's physiologic release of insulin and to allow flexibility regarding times when meals are consumed. A disadvantage of the regimen is the need for multiple injections.

47. How is hemoglobin A$_1$C (HbA$_1$C) helpful for monitoring glycemic control?

The *hemoglobin A$_1$C* level (also known as *glycosylated hemoglobin* or *A$_1$C*) is a hemoglobin–glucose combination formed nonenzymatically within the cell. Initially, an unstable bond is formed between glucose and the hemoglobin molecule. With time, this bond rearranges to form a more stable compound in which glucose is covalently bound to the hemoglobin molecule. The amount of the unstable form may rise rapidly in the presence of a high blood glucose level, whereas the stable form changes slowly and provides a time-average integral of the blood glucose concentration through the 120-day life span of the red blood cell. Thus glycohemoglobin levels provide an objective measurement of averaged diabetic control over time. Measurements are given as the percentage of hemoglobin that is glycated.

Rewers M, Pihoker C, Donaghue K, et al. Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes.* 2007;8(6):408–418.

48. Describe the goals of glycemic control.

Glycemic control in a patient with T1DM is assessed using the A$_1$C level. The goal for children and adolescents is **<7.5%**. This corresponds to blood sugars that are generally in the range of 80 to 180 mg/dL. Achieving good glycemic control requires rigorous and intensive attention to blood sugars; more frequent blood sugar monitoring is associated with better control. Blood sugar should ideally be checked upon waking, before all meals/snacks, before bedtime, and, at times, in the middle of the night. Blood sugars also need to be monitored more frequently around exercise and on sick days. Both of these situations can lead to unpredictable high and low blood sugars. It is recommended that the A$_1$C be checked every 3 months.

American Diabetes Association. Glycemic targets: standards of medical care in diabetes—2018. *Diabetes Care.* 2019;42(Suppl 1): S61–S79.

49. What current technologic advances are available to manage type 1 diabetes?

- **Insulin pumps** are composed of a pump, which holds the insulin, tubing, and a cannula, that is inserted under the skin every 2 to 3 days. This allows for the basal-bolus regimen to be carried out without multiple injections per day. The patient's carbohydrate ratios, correction factors, and basal settings (which can vary depending on time of day) are programmed into the pump.
- **Continuous glucose monitors (CGMs)** are sensors that are placed on the skin with a needle reaching into the interstitial fluid and providing a reading of the glucose concentration to a receiver every 5 to 15 minutes. The mean absolute relative difference (MARD) of these devices is about 10% from traditional finger-stick blood sugar checks. Many of the CGMs also allow for trends to be displayed, for example, whether the blood sugar is stable, rising, or falling.
- **Hybrid closed loops** are automated insulin delivery systems (some call this an "artificial pancreas"), which allow for integration of the CGM with the pump to increase the basal rate if the blood sugar is rising or to turn off the insulin if the blood sugar is falling.

Use of these devices requires a good understanding of the management of diabetes and commitment on the part of the patient and family to its proper use.

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de Bock M, McAuley SA, Abraham MB, et al. Effect of 6 months hybrid closed-loop insulin delivery in young people with type 1 diabetes: a randomised controlled trial protocol. *BMJ Open.* 2018;8(8):e020275.

Klonoff DC, Ahn D, Drincic A. Continuous glucose monitoring: a review of the technology and clinical use. *Diabetes Res Clin Pract.* 2017;133:178–192.

Bode BW, Kaufman FR, Vint N. An expert opinion on advanced insulin pump use in youth with type 1 diabetes. *Diabetes Technol Ther.* 2017;19(3):145–154.

50. Describe the role of nutrition and exercise in type 1 diabetes.

Proper *nutritional counseling* is a cornerstone of diabetes management. Families need to understand that children with type 1 diabetes should eat a healthy, well-balanced diet composed of fat, protein, and carbohydrates for normal growth and development. Extreme carbohydrate restriction is not advised; however, excessive carbohydrate intake can lead to hyperglycemia and weight gain. Ongoing guidance by a medical nutritionist who is well versed in the management of type 1 diabetes is essential to make sure a healthy meal plan is being followed and that carbohydrates are being appropriately dosed. *Exercise* remains challenging for those living with type 1 diabetes. Blood sugars can fluctuate widely during and after exercise, and hypoglycemia can occur hours after exercise is completed. Managing blood sugars around exercise requires a commitment to frequent blood sugar checks.

Blood glucose response to physical activity is highly variable based on activity type and when the activity is done in relation to insulin and food intake. Aerobic exercise in general will lead to lowering of blood sugars, whereas anaerobic exercise (weight lifting) may actually cause a rise in blood sugars. Patients should be counseled by their endocrinologists and diabetes educators on testing more frequently around exercise, taking frequent breaks to check blood sugars, and being vigilant for low glucose levels that may occur overnight after exercise. Adjustments in food and insulin boluses are often required around exercise.

Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol.* 2017;5(5):377–390.

51. What potential coexistent autoimmune conditions require screening in patients with T1DM?

There is an increased frequency of other autoimmune diseases in people with T1DM. The most common are **thyroid disorders**. These should be screened for soon after diagnosis and every 1 to 2 years thereafter—sooner if symptoms develop. **Celiac disease** should be screened for at diagnosis, then within 2 years, and then again after 5 years. Screening should occur sooner if symptoms develop or in patients with a first-degree relative with celiac disease. Other, less common autoimmune disorders include Addison disease, autoimmune hepatitis, and vitiligo.

American Diabetes Association. Comprehensive medical evaluation and assessment of comorbidities: standards of medical care in diabetes—2019. *Diabetes Care.* 2019;42(Suppl 1):S34–S45.

52. Define hypoglycemia in T1DM.

Hypoglycemia is defined in patients with T1DM as any blood sugar **<70 mg/dL** and should prompt treatment. Hypoglycemia, which may or may not be symptomatic, is a common and dangerous situation for those living with diabetes. Symptoms can include shakiness, sweating, pallor, hunger, and tachycardia. Severe symptoms include seizure, loss of consciousness, neurologic impairment, and even death.

53. How should hypoglycemia be treated?

Initial treatment should begin orally for *conscious patients* with a simple rapid-acting concentrated carbohydrate, such as sweetened fruit juice or glucose tablets. Weight-based dosing (0.3 to 0.6 mg/kg of glucose) can be utilized; 10 grams for children and 15 grams for adolescents. Four ounces (½ cup) of fruit juice contains 15 grams of carbohydrate. Blood sugar should be repeated in 15 minutes to be certain it is >70 mg/dL; treatment should be repeated until that threshold is reached. If the patient is *unconscious or seizing*, intramuscular (IM) glucagon should be administered. Children with diabetes should wear MedicAlert jewelry and should carry with them at all times treatment for low blood sugars; families and schools should be trained to use glucagon.

Gregory JM, Moore DJ, Simmons JH. Type 1 diabetes mellitus. *Pediatr Rev.* 2013;34(5):203–215.

54. What are the long-term complications of T1DM?

Long-term complications of diabetes include **macrovascular** and **microvascular disease**. Heart disease is a major complication of diabetes, particularly when poorly controlled. Blood pressure should be monitored at each routine visit and should be within age and sex norms. Lipids should be monitored after the child reaches 10 years of age. The goal low-density lipoprotein (LDL) in a child with T1DM is <100 mg/dL. Microvascular disease includes retinopathy, neuropathy, and nephropathy. The American Diabetes Association (ADA) outlines guidelines for the screening of these complications. Tight glycemic control and avoidance of smoking must be stressed at every visit.

American Diabetes Association. Microvascular complications and foot care: standards of medical care in diabetes—2019. *Diabetes Care.* 2019;42(Suppl 1):S124–S138.
Rawshani A, Rawshani A, Franzen S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med.* 2017; 376(15):1407–1418.

55. What pathophysiologic process characterizes type 2 diabetes (T2DM)?

T2DM is characterized by a **resistance to insulin action** accompanied by a **relative insulin secretory defect** in the absence of autoimmune markers.

56. Is the prevalence of T2DM in children increasing?

Previously rare in pediatrics, T2DM in children is increasing in incidence and prevalence. In the United States, there was a 38% increase in the prevalence of T2DM in children <19 years of age between 2002 and 2012. It is most common in nonwhite children and adolescents with a strong family history of T2DM. It is rarely seen before the onset of puberty.

Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. *N Engl J Med.* 2017;376(15):1419–1429.

57. How does T2DM differ in teenagers compared with adults?

- There is a more rapid decline in pancreatic β-cell function in teens: 20% to 35% per year, compared with 7% to 11% per year in adults. The need for insulin therapy occurs in an earlier time frame for teenagers.
- Teenagers with T2DM more commonly (6%) present with DKA at diagnosis, reflecting a more initial severe insulin deficiency.
- Complications of T2DM are accelerated in teenagers: albuminuria (indicative of impaired renal function) occurs in ≈6% within 5 years, 2.3% have end-stage renal failure by 10 years after diagnosis; retinopathy (as detected by microvascular changes) also appears earlier; the likelihood of hypertension can triple from 11% to 34% over a 4-year period.

Khattab A, Sperling MA. Obesity in adolescents and youth: the case for and against bariatric surgery. *J Pediatr.* 2019;207:18–22.

58. What historical and clinical features suggest type 2 rather than type 1 diabetes?

- **Obesity** is very common in children with T2DM; it is much less common in children with T1DM at diagnosis.
- **Age of onset:** T2DM only rarely presents before the onset of puberty; T1DM commonly presents in prepubertal as well as pubertal children.
- **Racial and ethnic minority groups,** particularly black, Mexican Americans, and Native Americans, are at higher risk for T2DM.
- **Family history** is usually strongly positive when a child develops T2DM; more than 50% of affected children have at least one first-degree relative with T2DM.
- **Acanthosis nigricans**, a marker of insulin resistance, is present in 90% of T2DM cases, most commonly on the posterior neck.
- **Hyperandrogenism** in girls is associated with insulin resistance and obesity. This is common in girls and young women with T2DM.
- **Differing symptoms:** Unlike patients with T1DM, most children and adolescents with T2DM will present without ketonuria (although up to 33% of children with T2DM will present with ketonuria).

Liu L, Hironaka K, Pihoker C. Type 2 diabetes in youth. *Curr Probl Pediatr Adolesc Health Care.* 2004;34(7):254–272.

59. What laboratory features are helpful to distinguish T1DM from T2DM?

Although classification can usually be made on the basis of clinical characteristics, measurement of levels of **fasting insulin** and **C-peptide** (low in T1DM; normal or elevated in T2DM) or **diabetes-associated autoantibodies** (positive in T1DM; absent in T2DM) may be useful to distinguish T1DM from T2DM. Be mindful that there can be overlap in the laboratory evaluation.

American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. *Diabetes Care.* 2018;41(Suppl 1):S13–S27.

60. Which pediatric patients should be screened for T2DM?

The ADA recommends screening beginning at 10 years of age (or earlier if puberty initiates <10 years). Screening should be performed using a fasting plasma glucose, oral glucose tolerance test, or hemoglobin A_1C for patients with the following risk factors:

- Body mass index >85th percentile for age and sex, *plus*
- Any *one or more* of following risk factors: positive family history in first- or second-degree relative; high-risk race/ethnicity (Native American, black, Hispanic, or Asian or Pacific Islander); presence of associated conditions (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome)
- Maternal history of diabetes or gestational diabetes during the child's gestation

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American Diabetes Association. Standards of medical care in diabetes—2018 abridged for primary care providers. *Diabetes Care.* 2018;41(Suppl 1):S16.

61. What is acanthosis nigricans?

Acanthosis nigricans is hyperpigmented and often highly rugated patches that are found most prominently in intertriginous areas, especially on the nape of the neck (Fig. 6.3). This is a marker of insulin resistance.

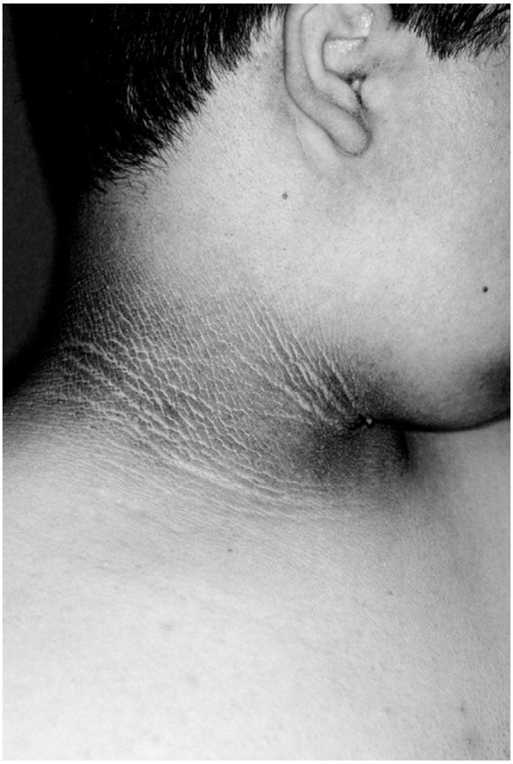

Fig. 6.3 Acanthosis nigricans in an adolescent male. (From Schachner LA, Hansen RC, eds. *Pediatric Dermatology*. 3rd ed. Edinburgh, Scotland: Mosby; 2003:915.)

62. How is T2DM diagnosed?

The diagnosis of diabetes is based on blood glucose level cutoffs, and the levels used are the same for T1DM and T2DM. The diagnosis is made when any of the following criteria are met:

- Random glucose concentration of $\geq$200 mg/dL (if accompanied by classic symptoms: polyuria, polydipsia, weight loss)
- Fasting ($>$8 hours) glucose concentration of $\geq$126 mg/dL
- Abnormal oral glucose tolerance test, defined as a glucose concentration of $\geq$200 mg/dL measured 2 hours after drinking 1.75 g/kg of glucose (with a maximum dose of 75 g)
- Hemoglobin A_1C $\geq$6.5%
  If results are near but over the diagnostic thresholds, repeat testing in 3 to 6 months is advised.

American Diabetes Association. Standards of medical care in diabetes—2018 abridged for primary care providers. *Diabetes Care.* 2018;41(Suppl 1):S15.

63. What is the treatment of T2DM in children?

- If the hemoglobin A_1C is $\leq$8.5%, initiate lifestyle changes (diet and exercise) and metformin.
- If marked hyperglycemia $\geq$250 mg/dL and hemoglobin A_1C values are over 8.5%, treatment with basal insulin should also be initiated. If hyperglycemia improves, insulin can be weaned over 2 to 6 weeks by slowly decreasing the insulin dose. For children over age 10 years, liraglutide (a glucagon-like peptide-1 receptor agonist) is approved to add to metformin with or without insulin if glycemic targets are not reached.

Tamberlane WV, Barrientos-Perez M, Fainberg U, et al. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med.* 2019;381(7):637–646.

American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2019. *Diabetes Care.* 2019;42(Suppl 1):S90–S102.

64. What is maturity-onset diabetes of the young (MODY)?

MODY is a rare cause of pediatric diabetes (1% to 4% of cases), but it is important to recognize, as it has implications for treatment and future offspring. It is the most common type of *monogenic diabetes,* which results from a single genetic mutation (as opposed to T1DM or T2DM, where the etiology appears to involve many genes, as well as environmental and/or lifestyle components). Forty different genetic subtypes of MODY have been identified, each with a different phenotype and pattern of inheritance, although most are autosomal dominant. MODY due to glucokinase genetic mutations, GCK-MODY (MODY 2), is the most common type found in pediatric MODY cases and is characterized by mild hyperglycemia usually requiring no treatment. Mutations in the hepatocyte nuclear factor-1 alpha (such as HNF1A-MODY [MODY 3]) are generally more progressive and will require treatment. Monogenic diabetes should be suspected in children/adolescents who have been diagnosed with type 1 or type 2 diabetes when:

- There is a strong family history of diabetes and the family is not obese
- Prolonged β-cell function with measurable C-peptide
- Lack of acanthosis or other metabolic markers
- Absence of diabetes autoantibodies

Rubio-Cabezas O, Greeley SAW, Polak, et al. ISPAD clinical practice consensus guidelines 2018: the diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes.* 2018;19(Suppl 27):47–63.

KEY POINTS: DIABETIC KETOACIDOSIS

1. The triad of metabolic derangement includes hyperglycemia, ketosis, and acidosis.
2. Abdominal pain can mimic appendicitis; hyperventilation can mimic asthma or pneumonia.
3. Initial bolus of insulin is no longer recommended.
4. Total-body potassium is usually significantly diminished.
5. Cerebral edema is the most common cause of morbidity and mortality in children with DKA.
6. If the sodium level begins to fall with fluid replenishment, beware of secretion of antidiuretic hormone and possible cerebral edema.
7. Bicarbonate therapy is usually not indicated for acidosis.

KEY POINTS: DIABETES MELLITUS TYPE 1

1. Destruction of pancreatic islet cells causes an absolute insulin deficiency.
2. Classic triad of symptoms includes polyuria, polydipsia, and polyphagia.
3. Tighter glucose control substantially lowers complication rates of retinopathy, nephropathy, and neuropathy.
4. Obtaining a hemoglobin A_1C (glycosylated hemoglobin) level is a standard way to assess average control during the previous 2 to 3 months.
5. Puberty is a time of increased insulin resistance, thereby requiring increased dosing.

KEY POINTS: DIABETES MELLITUS TYPE 2

1. Pathophysiology includes progressive insulin secretory defect on the background of insulin resistance.
2. Incidence is rising rapidly in association with increased rate of pediatric obesity.
3. Acanthosis nigricans (altered skin pigmentation and texture) associated with insulin resistance is common (found in 90% of cases).
4. Diagnosis is based on detecting hyperglycemia: fasting ($\geq$125 mg/dL), random with symptoms ($\geq$200mg/dL), or postprandial glucose challenge ($\geq$200 mg/dL), or via HbA_1C $>$6.5%.
5. Screen patients based on known risk factors (obesity, ethnicity, family history).

GROWTH DISTURBANCES

65. How do the growth rates of boys and girls differ?

In both boys and girls, the rate or velocity of linear growth begins to decelerate right after birth. In girls, this growth without acceleration continues until the age of about 11 years, at which time the adolescent growth spurt begins. For boys, the growth without acceleration continues until the age of about 13 years. The peak rate of increase in boys occurs at 14 years of age. Growth and growth rate charts are readily available from the Centers for Disease Control and Prevention website (www.cdc.gov/growthcharts).

66. What is the best predictor of a child's eventual adult height?

Midparental height. This is an estimate of a child's expected genetic growth potential based on parental heights (preferably measured rather than by history).

$$\textit{For girls}: ([\text{father's height} - 13\,\text{cm}] + [\text{mother's height}])/2$$
$$\textit{For boys}: ([\text{mother's height} + 13\,\text{cm}] + [\text{father's height}])/2$$

This gives the range (±5 cm) of expected adult height. The predicted height can be compared with the present height percentile, and any significant deviation can be a clue to an abnormal growth pattern in a child. It is important to remember that some forms of growth hormone deficiency are inherited, so one should not automatically assume that the short child with short parents has familial short stature.

67. When have most children achieved the height percentile that is consistent with parental height?

By the age of 2 years. Taking a boy's length at age 2 years and a girl's length at age 18 months and doubling them can obtain rough estimates of ultimate adult height.

68. When is a detailed evaluation for short stature warranted?

- Severe height deficit (less than first percentile for age)
- Abnormally slow growth rate (less than 10th percentile for bone age)
- Predicted height is significantly different from midparental height
- Body proportions are abnormal

Allen DB, Cuttler L. Short stature in childhood—challenges and choices. *N Engl J Med.* 2013;368(13):1220–1128.

69. What are the major categories of causes of short stature?

- **Familial** (for short children, ≤ 3 standard deviations, with very short parents, consider genetic forms of short stature)
- **Constitutional delay** ("late bloomer")
- **Chronic disease/treatment** (e.g., inflammatory bowel disease, chronic renal failure, renal tubular acidosis, cyanotic congenital heart disease)
- **Undernutrition**
- **Chromosomal/syndromic** (e.g., Turner [45,X], 18q-, trisomy 21, achondroplasia)
- **Endocrine** (e.g., hypothyroidism, growth hormone deficiency, hypopituitarism, hypercortisolism [endogenous and exogenous])
- **Psychosocial** (e.g., chaotic social situation, orphanage)
- **Intrauterine** (e.g., small for gestational age)

Genetic patterns and constitutional delay account for the largest percentage of known causes of short stature.

70. What factors influence growth rates in children?

A minimum of 6 months is needed for a meaningful height velocity, and 9 to 12 months is preferred due to seasonal variation. In summer months, growth hormone secretion is increased with resulting increase in height velocity. Infants and toddlers have a higher growth velocity that will eventually slow to a prepubertal rate by about age 5 years. The timing of adolescent pubertal growth spurts varies. Changes in weight can precede height changes. Growth rates that are consistently below the genetic potential or crossing percentiles downward after 2 years of age warrant careful consideration and possible investigation.

71. A 2.5-year-old is referred for slowed growth, but on follow-up measurements, the patient appears to be on track. What could explain this discrepancy?

It is important to be mindful of *measurement technique*. All babies should be measured on a flat hard surface with an inflexible board for the head and a moveable foot board. The baby should be relaxed and fully extended with the head in the Frankfort plane (line connecting the outer canthus of the eye and external auditory meatus perpendicular to the long axis of the trunk). Standing heights for those >2 years of age are best measured with an inflexible stadiometer or arm mount. Flexible arms or free-standing rulers are less accurate and require more frequent calibration. Children should be measured fully erect, with heels together and once again with the head in the Frankfort plane. Change in measurement between supine and standing can produce an artificial growth deceleration, as supine measurements are always longer than standing measures.

72. When evaluating a short child, why should you ask when the parents reached puberty?

The age at which puberty occurred in other family members may help identify children with constitutional delay because this entity tends to run in families. Most women will remember their age at menarche, and this age can be used as a reference for the age at which other pubertal events occurred. The strongest association for pubertal delay is between father and son. The most useful reference point for adult males is the age at which they reached adult height because almost all normal males will have reached their adult height by the age of 17 years (before high school graduation). Significant growth beyond this age suggests a history of pubertal delay.

73. When does the pubertal growth spurt occur?

For children with an average growth rate, pubertal growth begins earlier in girls. Mean age at the *initiation* of this spurt is 11 years for boys and 9 years for girls. *Peak* height velocity occurs at 13.5 years for boys and 11.5 years for girls. Peak velocity occurs at Tanner breast stage II to III for girls and Tanner testis stage III to IV for boys. Girls generally stop growing at an average of 14 years of age, but boys continue to grow until 17 years of age. The major hormone affecting growth cessation is estradiol in both girls and boys. The timing of the pubertal growth spurt may be earlier in certain ethnic groups and in very obese children. Assessment of short stature requires a determination of Tanner pubertal staging. On average, boys will grow 20 to 30 cm after the onset of puberty and girls between 15 and 25 cm.

Cheetham T, Davies JH. Investigation and management of short stature. *Arch Dis Child.* 2014;99(8):767–771.
Rogol AD, Roemmich JN, Clark PA. Growth at puberty. *J Adolesc Health.* 2002;31(6 Suppl):192–200.

74. Are upper to lower body ratios helpful for the diagnosis of growth problems?

Disproportionate short stature generally refers to an inappropriate ratio between truncal length and limb length (upper to lower segment ratio). Lower segment (limb length) is the distance from the superior border of the pubic bone to the floor surface. Height minus the lower segment gives the height of the upper segment (truncal length). In an infant, the head and trunk are quite long relative to the limbs, so the ratio of truncal length to limb length is about 1.7. Throughout childhood, this ratio declines, so that by 7 to 10 years of age this ratio is about 1.0. The adult ratio is 0.9.

An increased ratio is seen in bony dysplasias (e.g., achondroplasia, hypochondroplasia), hypothyroidism, gonadal dysgenesis, and Klinefelter syndrome (the patients are then tall in adolescence). Decreased ratios are seen in certain syndromes (e.g., Marfan syndrome), spinal disorders (e.g., scoliosis), and children who have been exposed to specific types of therapy (e.g., spinal irradiation).

Mehlman CT, Ain MC. Evaluation of the child with short stature. *Orthop Clin North Am.* 2015;46(4):523–531.
Halac I, Zimmerman D. Evaluating short stature in children. *Pediatr Ann.* 2004;33(33):170–176.

75. What laboratory studies should be obtained when evaluating short stature?

Extensive laboratory tests are generally not indicated unless the growth velocity is abnormally low or there is a change in height percentile discrepant with parental heights. Laboratory testing may include any or all of the following: complete blood count, urinalysis, chemistry panel, sedimentation rate, thyroxine, thyroid-stimulating hormone (TSH), insulin-like growth factor-1 (IGF-1), and IGF-binding protein-3 (IGFBP-3). Depending on the clinical history, testing might also be done for celiac disease, inflammatory bowel disease, renal tubular acidosis, or other occult conditions.

Random growth hormone levels are of little value because they are generally low in the daytime, even in children of average height. IGF-1 mediates the anabolic effects of growth hormone, and levels correlate well with growth hormone status. However, IGF-1 can also be low in nonendocrine conditions (e.g., malnutrition, liver disease).

IGFBP-3, which is the major binding protein for IGF-1 in serum, is also regulated by growth hormone. IGFBP-3 levels generally indicate growth hormone status and are less affected by nutritional factors than IGF-1. Many endocrinologists now use IGF-1 and IGFBP-3 as their initial screening tests for growth hormone deficiency. Further genetic testing, such as a karyotype, may be included.

Mehlman CT, Ain MC. Evaluation of the child with short stature. *Orthop Clin North Am.* 2015;46(4):523–531.
Cheetham T, Davies JH. Investigation and management of short stature. *Arch Dis Child.* 2014;99(8):767–771.

76. How does a growth chart help determine the diagnosis of failure to thrive?

If an infant is demonstrating deceleration of a previously established growth pattern or growth that is consistently less than the fifth percentile, the pattern of growth of head circumference, height, and weight can help establish the likely cause (Fig. 6.4). There are three main types of impaired growth:

- **Type I:** Retardation of weight with near-normal or slowly decelerating height and head circumference; most commonly seen in undernourished patients
- **Type II:** Near-proportional retardation of weight and height with normal head circumference; most commonly seen in patients with constitutional growth delay, genetic short stature, endocrinopathies, and structural dwarfism
- **Type III:** Concomitant retardation of weight, height, and head circumference; seen in patients with *in utero* and perinatal insults, chromosomal aberrations, and CNS abnormalities

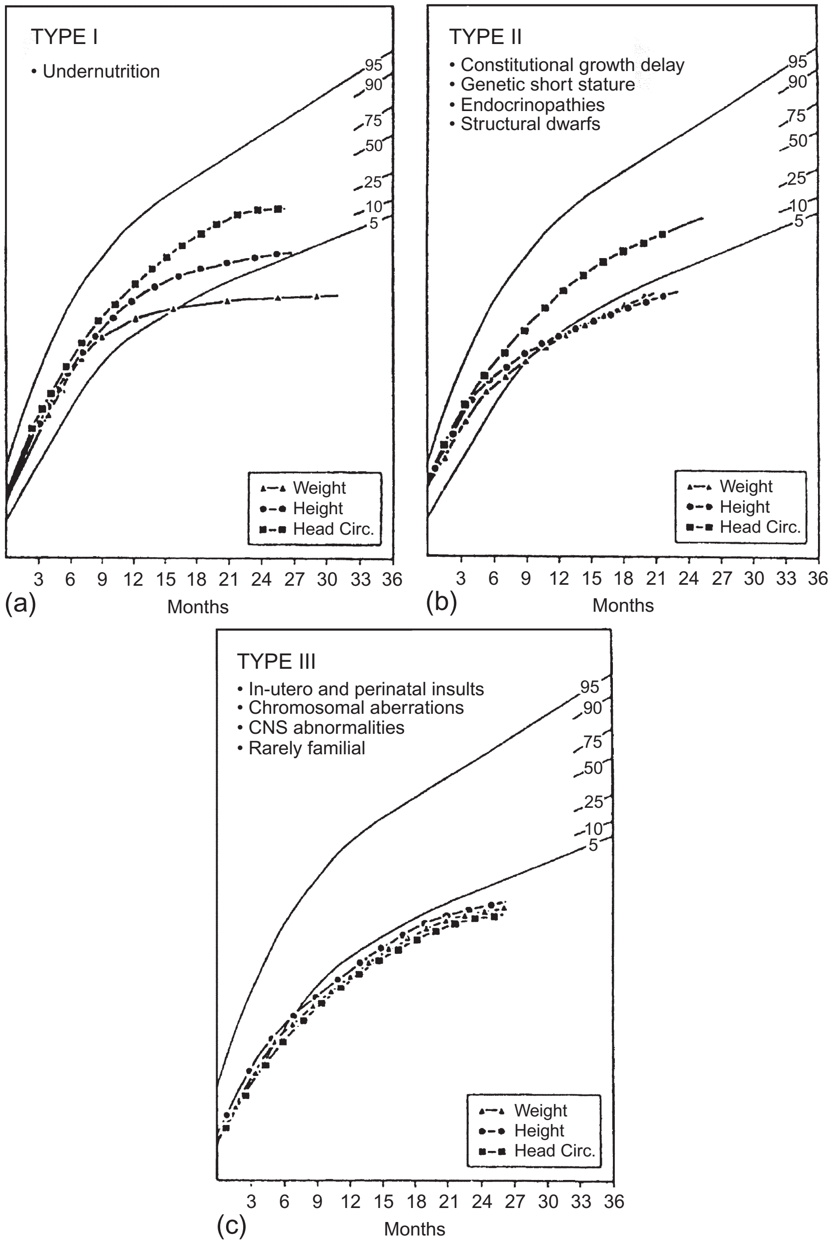

Fig. 6.4 Types I, II, and III of impaired growth. *CNS,* Central nervous system. (From Roy CC, Silverman A, Alagille DA. *Pediatric Clinical Gastroenterology*. 4th ed. St. Louis, MO: Mosby; 1995:4–8.)

77. How can one track growth in children who have spinal cord abnormalities or severe scoliosis?

There is an excellent 1:1 correlation between **span** (longest fingertip to longest fingertip measured across the nape of the neck) and height. Thus span is a useful proxy measure for height/length if it is not possible to get an accurate height. Height and rate of growth, when determined in this way, can be plotted on standard growth and velocity charts.

78. A 14-year-old girl is referred for short stature and lack of puberty and has an otherwise normal examination. What test may help diagnose the cause of her short stature?

A **karyotype** should be performed in all females evaluated for short stature to rule out Turner syndrome (TS). Although the classic features of TS include extra skin folds at the neck (webbed neck), lymphedema of the hands or feet, wide-spaced nipples, or history of congenital heart disease, there are many children who have otherwise normal examinations and may present with growth failure only. Treatment includes growth hormone at time of diagnosis in older children or growth deceleration in younger children and a possible need for induction of puberty when age appropriate.

79. What is a bone age?

Bone age is a measure of *somatic maturity* and *growth potential*. Standards of normal skeletal radiographic maturation are available, and these are based on the progression of ossification centers that occur at particular ages. A radiograph of the left hand and wrist is taken and compared with those standards to determine a patient's bone age. This result can be compared with chronologic age to gauge the remaining potential for growth. The interpretation of bone ages can be somewhat difficult and dependent on the pediatric experience of the radiologist.

80. Why is a bone age determination helpful for evaluating short stature?

A single bone age is of value for differentiating familial short stature and genetic diseases (in which bone age is normal) from other causes of short stature. A *delayed bone age* (>2 standard deviations below the mean) that correlates with the child's height age (age on growth chart at which the child's height would be at the fiftieth percentile) is suggestive of constitutional delay, whereas a *markedly delayed bone age* is suggestive of endocrine disease. Serial bone ages determined every 6 to 12 months are often helpful because in both the normal child and the child with constitutional delay, the bone age will advance in parallel with the chronologic age. In endocrine disease, the bone age falls progressively further behind the chronologic age. Bone age may be normal or delayed in patients with chronic disease, depending on the severity of disease, its duration, and the type of treatment used.

81. What features suggest constitutional delay as a cause of short stature?

- No signs or symptoms of systemic disease
- Bone age delayed up to 2 to 4 years but consistent with height age (age at which individual's height would plot on the fiftieth percentile)
- Period of poorest growth often occurring between the ages of 18 and 30 months, with steady linear growth thereafter (i.e., normal rate of growth for bone age)
- Parental or sibling history of delayed physical development
- Height prediction consistent with family characteristics

82. How is constitutional delay managed?

If the results of history, physical examination, and clinical laboratory evaluation are unremarkable, the child is seen once every 3 to 6 months for accurate height measurements and determination of growth velocity. A bone age test may be done yearly to assess the progression of bony maturation. In patients with constitutional delay, the rate of bone maturation should keep pace with the chronologic age. In children who are of mid- to late pubertal ages (girls >13 years; boys >14 years) but showing minimal or no signs of puberty, selective use of estrogen or testosterone supplementation to initiate puberty or additional assessment may be indicated.

83. Should growth hormone therapy be given to the normal child with idiopathic short stature?

The use of growth hormone in patients who do *not* have severe deficiency of growth hormone or IGF-1 is an area of controversy in pediatric endocrinology. Human growth hormone is most effective when administered subcutaneously on a daily basis. It does increase growth rate and modestly improves adult height (1.2 to 2.8 inches). The safety profile has been good, and the risk for short-term adverse events (such as intracranial hypertension or glucose intolerance) is very low. Long-term safety remains under study. Opponents argue that short stature is not a disease, appropriate therapeutic goals are ill-defined, and treatment amounts to "cosmetic endocrinology." The therapy is expensive, estimated in 2006 dollars to be about $52,000 per inch of height gained.

Grimberg A, Allen DB. Growth hormone treatment for growth hormone deficiency and idiopathic short stature: new guidelines shaped by the presence and absence of evidence. *Curr Opin Pediatr.* 2017;29(4):466–471.
Allen DB, Cuttler L. Short stature in childhood—challenges and choices. *N Engl J Med.* 2013;368(13):1220–1128.
Lee JM, Davis MM, Clark SJ. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *JAMA Pediatr.* 2006;160(3):263–269.

84. What are some common causes of tall stature?

Tall stature is defined as >2 standard deviations for mean height of age and sex.

Causes include genetic tall stature, familial early maturation, growth hormone excess, hyperthyroidism, precocious puberty, estrogen resistance, cortisol resistance, and the following syndromes: Beckwith-Wiedemann, fragile X, Klinefelter, Marfan, and Sotos.

85. What are the clinical manifestations of growth hormone excess?

Before puberty, the cardinal manifestations are an increase in growth velocity with minimal bone deformity and soft tissue swelling—a condition called *pituitary gigantism*. Hypogonadotropic hypogonadism and delayed puberty often coexist with growth hormone excess, and affected children exhibit eunuchoid body proportions. If the growth hormone excess occurs after puberty (after epiphyseal closure), the more typical features of acromegaly occur, including coarsening of the facial features and soft tissue swelling of the feet and hands. Growth hormone excess is rare in children.

KEY POINTS: GROWTH DISTURBANCES

1. Bone age is used as a diagnostic key: genetically determined short stature (bone age $=$ chronologic age) versus constitutional delay (bone age $<$ chronologic age).
2. Midline defects (e.g., single maxillary incisor, cleft lip/palate, micropenis) and short stature suggest hypopituitarism.
3. Random growth hormone levels are usually not helpful (due to pulsatile delivery during sleep); provocative testing is more reliable.
4. Family history is key. Use growth data about family to establish a pattern.
5. Short stature with overweight suggests endocrinopathy (adrenal, thyroid, or growth hormone deficiency).
6. 6. Growth hormone deficiency that appears during the first year of life is often associated with hypoglycemia; after the age of 5 years, it is associated with short stature.

HYPOGLYCEMIA

86. What is the definition of hypoglycemia?

There is no consensus as to the actual value that defines hypoglycemia. However, blood glucose >70 mg/dL at any age can be considered normal and a target for normoglycemia. A plasma glucose <60 mg/dL should be evaluated clinically. Hypoglycemia should be considered a medical emergency, as it can lead to permanent brain injury if untreated.

Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants and children. *J Pediatr.* 2015;167(2):238–245.

Ferry RJ Jr, Allen DB. Hypoglycemia. In Kappy MS, Allen DB, Geffner ME, eds. *Pediatric Practice: Endocrinology*. 2nd ed. New York: McGraw Hill; 2010:393–408.

87. What are the symptoms and signs of hypoglycemia?

Neuroglycopenic (insufficient supply of glucose to the brain) features include irritability, headache, confusion, unconsciousness, and seizure. *Adrenergic* (autonomic response to hypoglycemia) findings include tachycardia, tremulousness, diaphoresis, and hunger. Any combination of these signs and symptoms should lead to the measurement of the blood glucose level. In infants, symptoms can be subtle and can include (but are not limited to) poor feeding, irritability, hypothermia, or tachycardia or tachypnea. A high index of suspicion must be maintained.

Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants and children. *J Pediatr.* 2015;167(2):238–245.

88. What are the normal defenses against hypoglycemia?

The normal plasma glucose level is physiologically protected. At a blood sugar <85 mg/dL, **insulin is suppressed**. Once the blood sugar is below 70 mg/dL, **counterregulatory hormones** (glucagon, growth hormone, and cortisol) are released. With prolonged fasting, glucose utilization will be restricted to the brain; **ketone production** is essential and is used by skeletal and heart muscle. Thus measurement of ketones during an episode of hypoglycemia is an important part of any diagnostic workup.

89. What are the causes of hypoglycemia in the older infant or child?

The differential diagnosis is very extensive. Following is a brief outline of some of the possible etiologies that should be considered in the differential:

- Hyperinsulinism
- Insulinoma
- Postoperative (e.g., small bowel transplant or Nissen fundoplication)
- Diseases of glycogen storage or gluconeogenesis
- Disorders of fatty acid oxidation
- Ketotic hypoglycemia
- Deficiency of growth hormone, cortisol (Addison disease)
- Alcohol or salicylate intoxication
- Surreptitious use of insulin or blood glucose–lowering oral agents

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90. What physical examination findings suggest a possible etiology for hypoglycemia?

- **Hepatomegaly**: possible glycogen storage disorder
- **Midline facial and cranial defects** or **microphallus**: possible hypopituitarism (pituitary hormone deficiencies)
- **Large body size**: possible hyperinsulinism
- **Decreased subcutaneous tissue**: possible inadequate glucose stores

91. An unconscious 3-year-old girl is brought to the ED with a serum glucose concentration of 26 mg/dL. What other laboratory tests should be performed?

Blood and urine samples are vital. The first urine specimen obtained after the presentation of the child is of significant value, even if this cannot be gotten for several hours after the acute event. A *critical blood sample*—one obtained before any treatment has begun—is essential. Principal laboratory evaluations should include the measurement of the following: (1) the metabolic compounds associated with fasting adaptation, (2) the hormones that regulate these processes, and (3) drugs that can interfere with glucose regulation. It is strongly recommended that an extra purple-top and red-top tube of blood be drawn, if at all possible. The extra tubes of blood should be kept for additional analyses once the first battery of tests described next is available or after specific recommendations by a metabolic specialist.

Blood can be sent for measurement of the following:

- Markers of the principal regulatory hormones: insulin, growth hormone, and cortisol
- Markers of fatty acid metabolism: ketones (β-hydroxybutyrate and acetoacetate), free fatty acids, and total and free carnitine
- Markers of gluconeogenic pathways: lactate, pyruvate, and alanine

Urine can be sent for measurement of the following:

- Ketones
- Metabolic by-products associated with known causes of hypoglycemia (e.g., organic acids, amino acids)
- Toxicology screen, especially for alcohol and salicylates

Taken together, these tests provide valuable clues as to the cause. For example, low levels of ketones and free fatty acids suggest that fat was not appropriately mobilized. As a consequence, ketones were not formed by the liver. Those biochemical abnormalities are seen in hyperinsulinemic states and can be confirmed by documenting a high level of circulating insulin. Low urinary ketones also suggest an enzymatic defect in fatty acid oxidation. If the critical sample of blood/urine is not obtained at the time of presentation (before treatment), the child will require readmission to the hospital for a provocative fasting test.

Josefson J, Zimmerman D. Hypoglycemia in the emergency department. *Clin Pediatr Emerg Med.* 2009;10:285–191.

92. In patients with acute hypoglycemia, what are the treatment options?

The principal acute treatment is the provision of **glucose orally or intravenously**. If the patient is alert, 4 to 8 ounces of a sugar-containing liquid (e.g., orange juice, cola) may be given. If the patient is obtunded, IV glucose (2 to 3 mL/kg of $D_{10}W$ or 1 mL/kg of $D_{25}W$) should be administered rapidly. If venous access cannot be achieved promptly, glucose can be provided through a nasogastric tube because glucose is rapidly absorbed. The risk for prolonged hypoglycemia far outweighs the risk associated with the passage of a nasogastric tube in an obtunded patient. Subsequently, the blood sugar should be monitored closely and, if necessary, maintained by the constant infusion of glucose (6 to 8 mg/kg/min). Ten percent dextrose and water in an electrolyte solution given at about 1.5 times the maintenance dose approximates 6 to 8 mg/kg/min. Larger quantities of glucose may be necessary, and the blood sugar concentration should be closely followed.

Glucagon promotes glycogen breakdown. In settings in which glycogen stores have not been depleted (e.g., insulin overdose), 0.03 mg/kg (max dose of 1 mg) of glucagon IM or subcutaneously (SC) will raise blood glucose levels.

Glucocorticoids should not be used routinely. Their only clear indication is in known primary or secondary adrenal insufficiency. In other settings, they have little acute value and may cloud the diagnostic process. The decision to use glucocorticoids is somewhat dependent on the child's medical history (e.g., reasonable to use in the context of a history of prior CNS irradiation).

HYPOTHALAMIC AND PITUITARY DISORDERS

93. What clinical signs or symptoms suggest hypothalamic dysfunction?

The signs and symptoms of hypothalamic dysfunction are as variable as the processes controlled by the hypothalamus, ranging from disorders of hormonal production to disturbances of thermoregulation. Precocious or delayed sexual maturation represents the most common presentations of a hypothalamic endocrine abnormality in childhood. Diabetes insipidus, behavioral and cognitive disturbances, and excessive sleepiness are found in about one-third of patients with hypothalamic dysfunction and may be the first manifestation of disease. Eating disorders (obesity, anorexia, and bulimia) and convulsions are also reported. Dyshidrosis and disturbances of sphincter control (e.g., encopresis, enuresis) are occasionally seen.

94. List the intracranial processes that can interfere with hypothalamic-pituitary function.

- **Congenital:** Inherited deficiencies of gonadotropin-releasing factor, growth hormone–releasing hormone; syndromic (Laurence-Moon-Biedl and Prader-Labhart-Willi syndromes)
- **Structural:** Craniopharyngioma, Rathke pouch cyst, hemangioma, hamartoma
- **Infectious:** Meningitis and encephalitis
- **Tumors:** Glioma, dysgerminoma, ependymoma, Wegener granulomatosis, histiocytosis X
- **Trauma/toxic:** Surgical complications, motor vehicle accidents, sports-related injuries, radiation exposure, chemotherapy
- **Idiopathic**

95. What findings should prompt evaluation of the hypothalamic–pituitary hormone axis in an otherwise healthy child?

In children a **midline structural abnormality** such as midline cleft lip or palate, **absence of the corpus callosum**, or **solitary midline maxillary central incisor** can be associated with an embryologic malformation of the hypothalamic–pituitary axis.

96. What is the most common pituitary deficiency seen in children with craniopharyngioma?

Craniopharyngiomas arise from the anterior pituitary embryonic tissue. Findings on imaging include a mixed solid-cystic structure with calcifications. Although benign in nature, mass effect from tumor enlargement can lead to pituitary hormone deficiencies as well as impingement on the optic chiasm. **Growth hormone deficiency** is seen in approximately 75% of children.

Halac I, Zimmerman D. Endocrine manifestations of craniopharyngioma. *Childs Nerv Syst.* 2005;21(8-9):640–648.

97. Which tests are useful for studying suspected hypothalamic and pituitary malfunction?

Either MRI or CT is required to rule out structural pathology before searching for functional abnormalities.

Studies of the pituitary–hypothalamus may include any or all of the following:

- **Prolactin:** Random levels tend to be elevated in the presence of hypothalamic lesions. A normal level does not rule out CNS pathology. An elevated level may occur in an anxious or stressed child during venipuncture.
- **Growth hormone production tests** (see question 75): These tests are generally indicated only if the child's growth rate is subnormal. Growth hormone–releasing factor is now available for testing pituitary responsiveness. It has proved useful in some instances to differentiate pituitary causes of growth hormone underproduction from primary hypothalamic disease.
- **Gonadotropin-releasing hormone analogue (GnRHa) provocative test:** Random levels of luteinizing hormone and follicle-stimulating hormone are not generally helpful if one is searching for pituitary hypofunction. The results of the GnRHa test must be correlated with the age of the child because there are developmental changes in the response to GnRHa.
- **ACTH stimulation testing (Cortrosyn):** This test of adrenal production of cortisol is often used in determining whether there has been adrenal destruction or to demonstrate more subtle abnormalities in adrenal steroid hormonogenesis. The hypothalamic-releasing hormone, corticotrophin-releasing factor, is also available and can be used to examine the production of ACTH by the pituitary.
- **Simultaneous urine and serum osmolalities:** A normal serum osmolality and a concentrated urine osmolality tend to rule out DI. If these results are equivocal, a water deprivation test may be required.
- **Thyrotropin-releasing hormone (TRH)** is no longer available for provocative testing.

SEXUAL DIFFERENTIATION AND DEVELOPMENT

98. An infant is born with "ambiguous genitalia." What features of the history and physical examination are key in the evaluation?

Of note, the term *ambiguous genitalia* is largely antiquated. The contemporary terminology is *disorder of sexual differentiation* (DSD). This term is thought to more accurately suggest causation rather than consequence and to be less pejorative in discussions with families and nonmedical lay people.

- ***History:*** One should search for evidence of maternal androgen excess (hirsutism during pregnancy) or androgen ingestion (rare now, but common in the 1960s with certain progestational agents), other hormonal use (e.g., for infertility or endometriosis), alcohol use, parental consanguinity, previous neonatal deaths, or a family history of previously affected children.
- ***Physical examination:*** The presence of a gonadal structure in the labioscrotal fold strongly implies the presence of some form of testicular tissue. Gonads containing both ovarian and testicular components (ovotestes) have been found in the inguinal canal. However, it is rare to find an ovary in the inguinal canal. In the absence of a palpable gonad, no conclusions can be drawn regarding probable chromosomal sex. The size of the phallic structure and the location of the urethral meatus provide no information about genetic makeup. However, phallic size and function may be important considerations when determining the sex the child will be assigned.

The presence of *midline abnormalities* (e.g., cleft palate) suggests hypothalamic or pituitary dysfunction, whereas congenital anomalies such as imperforate anus suggest structural derangements. A digital rectal examination will confirm the patency of the anus and may allow palpation of the uterus. In infants and young children, ultrasound is the best way to identify intra-abdominal structures and can often be helpful in confirming the presence or absence of müllerian structures and gonads. Other anomalies should be noted because disorders of genital development are often associated with other developmental disorders or syndromes.

Davies JH, Cheetham T. Recognition and assessment of atypical and ambiguous genitalia in the newborn. *Arch Dis Child.* 2017; 102(10):968–974.

McCann-Crosby B, Sutton VR. Disorders of sexual development. *Clin Perinatol.* 2015;42(2):395–412.

99. What are the causes of a DSD?

- **Undervirilized male** (XY karyotype):
  - *Androgen resistance:* complete (testicular feminization)
  - *Partial defects of androgen synthesis:* 3-β-hydroxysteroid dehydrogenase deficiency, 5-α-*reductase deficiency*
- **Virilized female** (XX karyotype):
  - *Excess androgen:* congenital adrenal hyperplasia, 21-hydroxylase deficiency, 3-β-*hydroxysteroid* dehydrogenase deficiency
  - *Maternal androgen exposure:* medication, virilizing adrenal *tumor*
- **Intersex** (mosaic karyotypes; e.g., XO/XY)
- **Structural abnormalities**

Houk CP, Lee PA. Consensus statement on terminology and management: disorders of sex development. *Sex Dev.* 2008;2(4-5):172–180.

MacLaughlin DT, Donahoe PK. Sex determination and differentiation. *N Engl J Med.* 2004;350(4):367–378.

100. Which studies are essential for the evaluation of a DSD?

- **Ultrasonography:** This test is the most helpful for identifying internal structures, particularly the uterus and occasionally the ovaries. The absence of a uterus suggests that testes were present early in gestation and produced müllerian-inhibiting factor, thereby causing regression of the müllerian-derived ducts and thus the uterus. The injection of contrast medium into the urethrovaginal openings will often demonstrate a pouch posterior to the fused labioscrotal folds. Occasionally, the cervix and cervical canal will be highlighted by this study as well.
- **Chromosomal analysis:** Obviously, this is useful for predicting gonadal content. There are a number of highly specialized and sensitive genetic tests to confirm the presence or absence of X or Y chromosomal material. A geneticist should always be consulted in infants with a DSD.
- **Measurement of adrenal steroids (17-hydroxyprogesterone, 11-deoxycortisol, 17-hydroxypregnenolone):** 17-Hydroxyprogesterone (17-OHP) is the precursor that is elevated in the most common variety of CAH associated with a DSD (21-hydroxylase deficiency). A 17-OHP is included on most state newborn screens; false-positive tests are common.
- **Measurement of testosterone and dihydrotestosterone (DHT):** Testosterone and DHT should be measured no sooner than the third day of life because of normal physiologic variation in the newborn. There is another peak between 30 and 60 days of age followed by a decline to prepubertal levels.

It is very important to have input from staff with expertise in this area, including a geneticist, a pediatric endocrinologist, and a pediatric urologist. It is also essential that this group synthesize information after all data are available and that it be communicated to the family by a single spokesperson.

Davies JH, Cheetham T. Recognition and assessment of atypical and ambiguous genitalia in the newborn. *Arch Dis Child.* 2017; 102(10):968–974.

Hiort O, Bimbaum W, Marshall L, et al. Management of disorders of sex development. *Nat Rev Endocrinol.* 2014;10(9):520–529.

Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Pediatrics.* 2006;118(2):e488–e500.

101. What major criteria are used to define a micropenis?

To be classified as a *micropenis,* the phallus must meet two major criteria:

1. The phallus must be normally formed, with the urethral meatus located on the head of the penis and the penis positioned in an appropriate relationship to the scrotum and other pelvic structures. If these features are not present, then the term *micropenis* should be avoided.
2. The phallus must be more than 2.5 standard deviations below the appropriate mean for age. For a term newborn, a micropenis is defined as a stretched penile length of ≤2 cm.

It is essential that the phallus be measured appropriately. This entails the use of a rigid ruler pressed firmly against the pubic symphysis, depressing the suprapubic fat pad as much as possible. The phallus is grasped gently by its lateral margins and stretched. The measurement is taken along the dorsum of the penis. Note should also be made of the breadth of the phallic shaft. Micropenis must be recognized early in life so that appropriate diagnostic testing can be done.

Lee PA, Mazur T, Danish R, et al. Micropenis. I. Criteria, etiologies and classification. *Johns Hopkins Med J.* 1980;146(4):156–163.

102. What are the main concerns to be addressed during the initial evaluation of a 1-month-old infant with micropenis?

1. **Is there a defect in the hypothalamic–pituitary–gonadal axis?** Specific tests include the measurement of testosterone, DHT, luteinizing hormone, and follicle-stimulating hormone. Because circulating levels of these hormones are normally quite high during the neonatal period, the measurement of random levels during the first 2 months of life may be useful for identifying diseases of the testes and pituitary. Beyond 3 months of age, the tests are generally not useful because the entire axis becomes quiescent and remains so until late childhood. Depending on the patient's age, provocative tests may be necessary, including the following: (1) repetitive testosterone injection to evaluate the ability of the penis to respond to hormonal stimulation, (2) the use of human chorionic gonadotropin as a stimulus for testosterone and DHT production by the testes, and (3) leuprolide administration to examine the responsiveness of the pituitary to stimulation. The trial of testosterone therapy is especially important because it indicates whether phallic growth is possible.
2. **Does a possible pituitary deficiency involve other hormones?** Isolated growth hormone deficiency, gonadotropin deficiency, and panhypopituitarism have been associated with micropenis. The presence of hypoglycemia, hypothermia, and direct hyperbilirubinemia in a child with micropenis should lead one to search for other pituitary hormone deficits and structural abnormalities of the CNS (e.g., septo-optic dysplasia).
3. **Is there a renal abnormality?** Because of the association of genital and renal abnormalities, it is prudent to obtain an abdominal and pelvic ultrasound to better define the internal anatomy.

103. What terms are used to describe precocious sexual development?

The terms used to describe precocious puberty reflect the fact that normal puberty is an orderly process by which female children are feminized and male children masculinized. The development of breast tissue without pubic hair is called *premature thelarche*. If pubic hair subsequently develops, the term *precocious puberty* is used. If pubic hair develops without breast tissue, it is *premature pubarche.* Because pubic hair development in the female is thought to be the result of adrenal androgens, the term *premature adrenarche* is commonly used. The term *premature adrenarche* is also used if the development of hair is accompanied by a rise in adrenal androgens consistent with pubertal state Tanner II. If the pubertal changes are early and appear to proceed in the orderly fashion of breast budding, pubic hair development, growth spurt, and, finally, menstruation, the term *true precocious puberty* is used.

104. Boys or girls: Who is more likely to have an identifiable cause for precocious puberty?

Although precocious puberty occurs much more frequently in girls (80% of cases are girls), **boys** are more likely to have identifiable pathology. As a general rule, the younger the child and the more rapid the onset of the condition, the greater the likelihood of detecting pathology.

105. A 7.5-year-old girl develops breast buds and pubic hair. Is this normal or precocious?

Precocious puberty is the appearance of physical changes associated with sexual development earlier than normal. Traditionally this has been the development of breasts in girls who are <8 years and testicular enlargement in boys who are <9 years. In 1997, an office-based study of 17,000 healthy 3- to 12-year-old girls revealed that puberty was occurring, on average, 1 year earlier in white girls and 2 years earlier in black girls and suggested a revision of guidelines for the ages at which precocious puberty should be investigated. Many experts now recommend that an evaluation for precocious puberty of girls need not be undertaken for white girls >7 years or black girls >6 years with breast and/or pubic hair development. However, this remains controversial over concerns that a lower threshold for diagnostic evaluation might prevent earlier identification of children with a treatable condition. Therefore the timing of evaluation is a subject of ongoing debate. The recommendations for boys remain that investigations for pathologic etiologies be undertaken if pubertal changes begin before the age of 9 years.

Klein DA, Emerick JE, Sylvester JE, Vogt KS. Disorders of puberty: an approach to diagnosis and management. *Am Fam Physician.* 2017;96(9):590–599.

Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. 2008;*Pediatrics.* 2008;121(Suppl):S172–S191.

Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings Network. *Pediatrics.* 1997;99(4):505–512.

106. Breast buds are noted on a 2-year-old girl. Is this worrisome?

Premature thelarche, or the development of breast buds, is the most common variation of normal pubertal development. A form of mild estrogenization, it typically occurs between the ages of 1 and 3 years. It is usually benign and should not be associated with the onset of other pubertal events. Precocious puberty, rather than simple premature thelarche, should be suspected if the following occur:

- Breast, nipple, and areolar development reach Tanner stage III (i.e., continued progression is of concern).

- Androgenization with pubic and/or axillary hair begins.
- Linear growth accelerates.
- Advancement of bone age is found.

Ongoing parental observation and periodic reexamination are all that are required if there are no signs of progression.

107. Which aspects of the physical examination are particularly important when evaluating a patient with precocious puberty?

- **Evidence of a CNS mass:** Examination of the optic fundus for possible increased intracranial pressure; visual field testing for evidence of optic nerve compression by a hypothalamic or pituitary mass
- **Evidence of androgenic influence:** Presence of acne and facial and axillary hair; increased muscle bulk and definition; extent of other body or pubic hair; in boys, increased scrotal rugation accompanied by thinning and pigmentation and penile elongation; in girls, clitoromegaly
- **Evidence of estrogenic influence:** Size of breast tissue and nipple and areolar contouring; vaginal mucosa color (increased estrogen causes cornification of vaginal epithelium with a color change from prepubertal shiny red to a more opalescent pink); labia minor (become more prominent and visible between the labia majora as puberty progresses); presence of vaginal discharge
- **Evidence of gonadotropic stimulation:** Testicular enlargement of >2.5 cm in length or >4 mL in volume (preferably measured using a Prader orchidometer of labeled volumetric beads); pubertal development without testicular enlargement usually suggests adrenal pathology
- **Evidence of other mass:** Asymmetrical testicular enlargement; hepatomegaly; abdominal mass

108. Which radiologic and laboratory tests are indicated for the evaluation of precocious puberty?

Radiologic evaluation

- *Bone age*: This study helps determine the duration of exposure to the elevated sex hormone. A significantly advanced bone age compared with the chronologic age suggests long-term exposure.
- *Abdominal and pelvic ultrasound:* In boys, this test identifies possible adrenal or hepatic masses; in girls, it identifies adrenal masses, ovarian masses, or cysts. Increased uterine size and echogenicity suggest endometrial proliferation in response to circulating estrogen.
- *Head CT or MRI:* This evaluation is useful in identifying pituitary or hypothalamic abnormalities.

Laboratory evaluation

- Obtain early morning luteinizing hormone, follicle-stimulating hormone, estradiol, testosterone levels, and thyroid function tests.
- Adrenal steroid levels (17-hydroxyprogesterone, androstenedione, and cortisol): More extensive testing may be needed in a virilized child if the initial studies are normal.
- Use provocative testing of the hypothalamic–pituitary axis (using a synthetic GnRHa) or of the adrenal gland (using a synthetic ACTH), especially in the child with slight but progressive pubertal changes.

THYROID DISORDERS

109. When should one check thyroid function tests in a child?

Diseases of the thyroid represent a heterogeneous group of disorders. There are no standard thyroid function studies that are appropriate for all children. AAP guidelines do not support routine biochemical thyroid evaluation in all children. However, the choice of laboratory tests should be based on the results of a careful history and physical examination, as well as known associated disorders (e.g., trisomy 21, TS, medication related).

110. What thyroid function tests should be utilized for suspected hyperthyroidism?

A **TSH level** and a **thyroxine level (total T_4 or free T_4)** should be obtained. Compared with total T_4, the free T_4 is the biologically active component and theoretically is a better measure of thyroid function. TSH suppression is probably the most sensitive indicator of hyperthyroid status. If the patient is symptomatic and has a suppressed TSH level with a normal T_4 level, it will be necessary to obtain a triiodothyronine (T_3) radioimmunoassay because T_3 thyrotoxicosis does occur. If the patient is asymptomatic but has an elevated T_4 level, some measure of binding capacity should be obtained (e.g., a T_3 uptake).

Hanley P, Lord K, Bauer AJ. Thyroid disorders in children and adolescents: a review. *JAMA Pediatr.* 2016;170(10):1008–1019.

111. What thyroid function tests should be utilized for suspected hypothyroidism?

The laboratory evaluation consists of the **quantitation of T_4** (total T_4 or free T_4) and **TSH**. A low T_4 level and an elevated TSH level are diagnostic of hypothyroidism.

Hanley P, Lord K, Bauer AJ. Thyroid disorders in children and adolescents: a review. *JAMA Pediatr.* 2016;170(10):1008–1019.

112. What are common thyroid findings in obese children?

Routine thyroid function testing in obese children should only be considered if the growth rate is below what is expected or if there are other signs and symptoms of hypothyroidism/hyperthyroidism. Both TSH and T_3 are mildly increased in obese compared with lean individuals.

113. What signs and symptoms in an infant suggest congenital hypothyroidism?

See Table 6.3.

Table 6.3 Symptoms and Signs of Hypothyroidism in Infancy

SYMPTOMS	SIGNS
Lethargy	Hypotonia, slow reflexes
Poor feeding	Jaundice (prolonged)
Constipation	Mottling
Poor weight gain	Distended abdomen
Cold extremities	Acrocyanosis
Hoarse cry	Coarse features
	Large fontanels, wide sutures

114. What causes congenital hypothyroidism?

- *Primary*: agenesis or dysgenesis, ectopic, dyshormonogenesis
- *Secondary*: hypopituitarism, hypothalamic abnormality
- *Other*: transient, maternal factors (e.g., goitrogen ingestion, iodide deficiency)

The most common cause of permanent primary congenital hypothyroidism is thyroid dysgenesis, or failure of the gland to develop properly. Ectopic thyroid gland location accounts for two-thirds of thyroid dysgenesis, followed by aplasia or hypoplastic gland. The second most common cause is thyroid dyshormonogenesis, which is a defect in thyroid hormone production. Thyroid dysgenesis accounts for 85% of permanent primary congenital hypothyroidism; inborn errors of thyroid hormone biosynthesis comprise 10% to 15% of cases.

Wassner AJ. Congenital hypothyroidism. *Clin Perinatol.* 2018;45(1):1–18.
LaFranchi S. Approach to diagnosis and treatment of neonatal hypothyroidism. *J Clin Endocrinol Metab.* 2011;96(10):2959–2967.

115. How effective are screening programs for congenital hypothyroidism?

Screening programs correctly identify 90% to 95% of children who are affected with congenital hypothyroidism. Screening programs are most likely to miss infants with large ectopic glands, those with partial defects in thyroidal hormone biosynthesis, and those with secondary (pituitary or hypothalamic) disease. If an infant presents with a clinical picture of hypothyroidism and has had a normal newborn screen, it is important to realize that the false-negative rate of the screening is up to 10%.

Kilberg MJ, Rasooly IR, LaFranchi SH, et al. Newborn screening in the US may miss mild persistent hypothyroidism. *J Pediatr.* 2018;192:204–208.
Grüters A, Krude H. Detection and treatment of congenital hypothyroidism. *Nat Rev Endocrinol.* 2011;8(2):104–113.

116. What are the risks of delaying treatment for congenital hypothyroidism?

Therapy should begin as early as possible because outcome is related to the time treatment is started. Because less than 20% of patients will have distinctive clinical signs at 3 to 4 weeks of age, screening is now performed on all newborns in the United States at 2 to 3 days of age, and most affected children are started on therapy before they are 1 month old. Many pediatricians and screening programs undertake a second screen at 2 weeks of age to ensure that children with treatable conditions are not missed. The prognosis for intellectual development is directly related to the amount of time from birth to the initiation of therapy, and there is an inverse relationship between age of diagnosis/treatment and intelligence quotient (IQ). In a literature review of 11 studies that evaluated starting treatment at an earlier age (12 to 30 days of life) compared with a later age (>30 days of life), infants started at an earlier age averaged 15.7 IQ points higher than infants started at a later age.

Wassner AJ. Congenital hypothyroidism. *Clin Perinatol.* 2018;45(1):1–18.
LaFranchi SH. Approach to the diagnosis and treatment of neonatal hypothyroidism. *J Clin Endocrinol Metab.* 2011;96(10):2959–2967.
LaFranchi SH, Austin J. How should we be treating children with congenital hypothyroidism? *J Pediatr Endocrinol Metab.* 2007;20(5):559–578.

117. What are common medications that can interfere with thyroid function?

- *Decrease T_4 synthesis or secretion*: propylthiouracil, methimazole, lithium, iodide, amiodarone
- *Increased T_4 release*: iodide, amiodarone
- *TSH suppression*: glucocorticoids, dopamine, somatostatin
- *Increased metabolism of thyroxine*: antiseizure medications, rifampin
- *Increased thyroxine-binding globulin levels*: estrogen (oral contraceptives)

118. A suspected goiter (diffuse enlargement of the thyroid gland) is noted during a routine examination of an asymptomatic 7-year-old boy. What should be the course of action?

The evaluation of a child with goiter (Fig. 6.5) is generally straightforward. In the absence of signs of thyroidal disease, history should be obtained regarding recent exposure to iodine or other halogens. A family history should be obtained regarding thyroidal disease, because thyroiditis tends to run in families. The initial laboratory evaluation typically includes T_4, TSH, and antithyroid antibodies. If there is discrete nodularity within the thyroid or the gland is either rock hard or tender, further diagnostic evaluation (ultrasound, CT) may be indicated. Otherwise, routine imaging is not indicated. Parathyroid enlargement or lymphoma may be misdiagnosed as goiter.

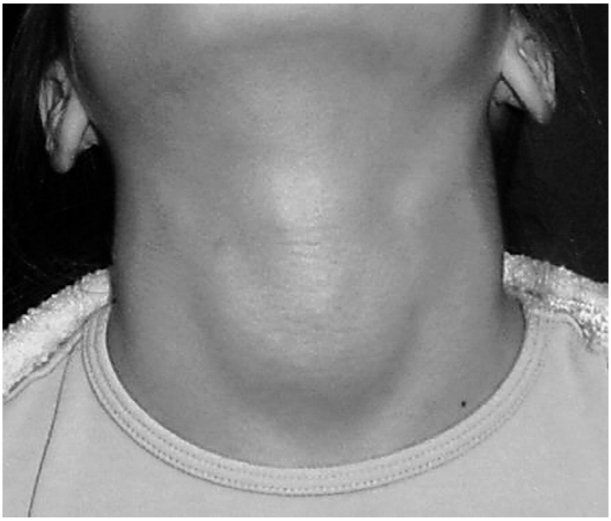

Fig. 6.5 Goiter. Note the enlarged thyroid gland in a patient with Hashimoto thyroiditis, easily visualized with neck extension. (From Zitelli BJ, McIntire SC, Nowalk AJ: *Atlas of Pediatric Physical Diagnosis*. 6th ed. Philadelphia, PA: Saunders; 2012:369-400.)

119. What is the most common cause of acquired hypothyroidism in childhood?

The most common cause is **chronic lymphocytic thyroiditis**, also called *Hashimoto thyroiditis* or *autoimmune thyroiditis,* which usually occurs in early to midpuberty. Its incidence during adolescence is about 1% to 2%. The female-to-male ratio is 2:1.

Counts D, Varma SK. Hypothyroidism in children. *Pediatr Rev.* 2009;30(7):251–257.

120. What is the most common clinical presentation of Hashimoto thyroiditis?

Although symptoms of hypothyroidism or hyperthyroidism may be present, most pediatric patients are **asymptomatic**, and the condition is detected by the presence of **goiter**. The diagnosis of Hashimoto thyroiditis is primarily based on the demonstration of antithyroid antibodies. Clinical manifestations may include a linear growth decline, fatigue, constipation, poor school performance, irregular menstrual periods, and cold intolerance.

Counts D, Varma SK. Hypothyroidism in children. *Pediatr Rev.* 2009;30(7):251–257.
Pearce EN, Farwell AP, Braverman LE. Thyroiditis. *N Engl J Med.* 2003;348(26):2646–2655.

121. What other autoimmune diseases are associated with chronic lymphocytic thyroiditis?

Adrenal insufficiency, diabetes mellitus, juvenile idiopathic arthritis, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenia purpura, and autoimmune polyendocrine syndrome (type II).

122. What does a normal free T_4 and elevated TSH suggest?

Hypothyroidism is diagnosed with *elevated* TSH and *low* free T_4 levels. Children and adolescents with an *elevated* TSH and a *normal* free T_4 level may have **subclinical hypothyroidism**. A concern is whether a patient will later progress to overt hypothyroidism. In this setting, many experts advise testing for antithyroid antibodies, as well as repeat testing, in 4 to 6 weeks. Positive antibody testing is indicative of autoimmune thyroiditis and an increased risk for clinical hypothyroidism. Children with persistence and antibody-negative testing can be evaluated for mutations of the TSH receptor gene, which has been found in up to 29% of those with non-autoimmune subclinical hypothyroidism. Of note, obese children and adolescents commonly have mildly elevated TSH and normal T_4 levels, with TSH levels normalizing when weight loss has occurred.

Peeters RP. Subclinical hypothyroidism. *N Engl J Med.* 2017;376(26):2556–2565.

Lazar L, Frumkin RB, Battat E, et al. Natural history of thyroid function tests over 5 years in a large pediatric cohort. *J Clin Endocrinol Metab.* 2009;94(5):1678–1682.

Nicoletti A, Bal M, DeMarco G, et al. Thyrotropin-stimulating hormone receptor gene analysis in pediatric patients with non-autoimmune subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2009;94(11):4187–4194.

123. What is the most common cause of hyperthyroidism in children?

More than 95% of hyperthyroidism cases are due to **Graves disease**, a multisystem disease that is characterized by hyperthyroidism, infiltrative ophthalmopathy, and, occasionally, an infiltrative dermopathy. The features of this disease may occur singly or in any combination. In children, the ophthalmopathy appears to be less severe and the dermopathy is rare; the full syndrome may never develop. There has been a tendency to use the terms *Graves disease, thyrotoxicosis,* and *hyperthyroidism* interchangeably, but there are other causes of hyperthyroidism in childhood (e.g., factitious).

Srinivasan S, Misra M. Hyperthyroidism in children. *Pediatr Rev.* 2015;36(6):239–248.

Léger J. Graves' disease in children. *Endocr Dev.* 2014;26:171–182.

124. In addition to Graves disease, what conditions may cause hyperthyroidism?

- **Excess TSH:** TSH-producing tumor (these are extraordinarily rare in children)
- **Thyroid autonomy:** Adenoma, multinodular goiter, activating mutations of G proteins (e.g., McCune-Albright syndrome)
- **Thyroid inflammation:** Subacute thyroiditis, Hashimoto thyroiditis
- **Exogenous hormone:** Medication, ectopic production

125. What are the typical features of hyperthyroidism that occur as a result of Graves disease?

- ***History:*** The onset of symptoms is usually gradual, with increasing emotional lability, shortened attention span, and deteriorating school performance. Sleep disturbance, nervousness, headache, and weight loss despite increased appetite may be noted, as well as easy fatigability and heat intolerance. Observation of the child's behavior while the history is being obtained from the parent is often instructive.
- ***Physical examination:*** Weight may be low for height, and many children will be tall for age and genetic potential. Some children will have an acceleration in growth rate at the same time that their behavior begins to deteriorate. The pulse rate is usually inappropriately high for age. A widened pulse pressure or an elevated blood pressure is often noted, although this is a more variable finding in children than in adults.

126. What causes Graves disease?

Graves disease is an *autoimmune disorder* in which TSH receptor antibodies bind to the TSH receptor, resulting in the stimulation of thyroid hormone production and subsequent hyperthyroidism. Most thyroid receptor antibodies belong to the IgG class. The general name used for these antibodies is human thyroid-stimulating immunoglobulins (HTSI or TSI). These were formerly called *long-acting thyroid stimulators (LATS).*

127. Why does exophthalmos occur in Graves disease?

Exophthalmos is a bulging of the eye anteriorly (Fig. 6.6). The reason is unknown, but several facts suggest an autoimmune process:

- Histologic studies reveal lymphocytic infiltration of the retrobulbar muscles.
- Circulating lymphocytes are sensitized to an antigen that is unique to the retrobulbar tissues.
- The thyroglobulin–antithyroglobulin antibody complexes found in patients with Graves disease bind specifically to the extraorbital muscles. There may be a separate class of antibodies that is responsible for changes in the retrobulbar muscles.

Bahn RS. Graves' ophthalmopathy. *New Engl J Med.* 2010;362(8):726–738.

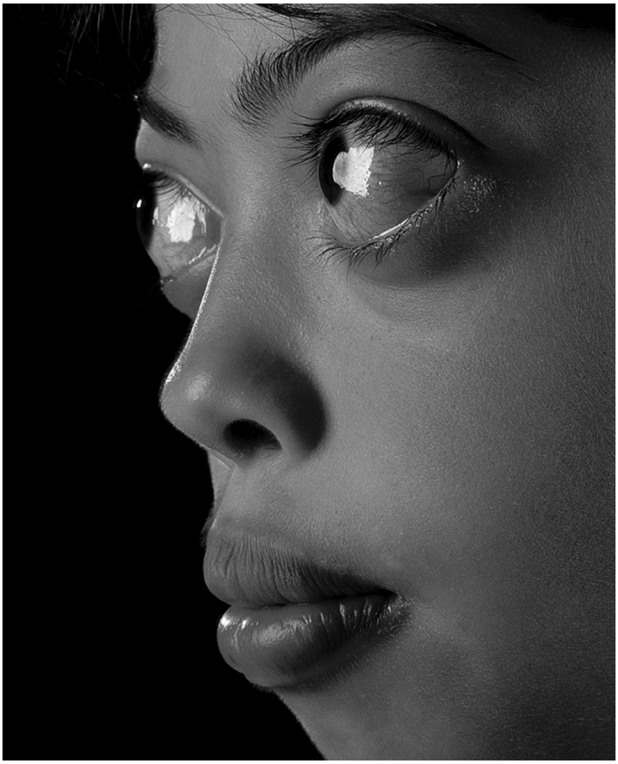

Fig. 6.6 Exophthalmos in a young woman with Graves disease. (From Moshang T Jr. *Pediatric Endocrinology: The Requisites in Pediatrics*. Philadelphia, PA: Elsevier Mosby; 2005:7.)

128. What treatment options are available for children with Graves disease?

The three types of therapy are antithyroid medication, radioactive (^{131}I) ablation, and subtotal thyroidectomy.

129. What are the principal modes of actions and the side effects of medications used to treat Graves disease?

The **thioamide derivatives**—*propylthiouracil* and *methimazole*—have historically been the keystones of long-term management. However, their effective onset of action is slow because they block the synthesis but not the release of thyroid hormone. **Beta blockers** (propranolol, atenolol) are useful for treating many of the β-adrenergic effects of hyperthyroidism. It is used during the acute management of Graves disease but should be discontinued when the thyroid disease is controlled. **Iodide** (which can transiently block thyroid hormone release) and **glucocorticoids** are useful stopgap medications while awaiting the inhibitory effects of the thioamides; they are generally used only when the patient is acutely symptomatic (i.e., thyroid storm).

The thioamides are associated with side effects, the most serious of which have been a lupus-like syndrome involving the lungs or liver, thrombocytopenia, neutropenia, agranulocytosis, and hepatitis with elevated transaminase levels. The association of propylthiouracil and severe liver failure led to the issuing of a black box warning from the Food and Drug Administration in 2010, with methimazole now the preferred antithyroid medication option.

DeLuca F, Valenzise M. Controversies in the pharmacological treatment of Graves' disease in children. *Expert Rev Clin Pharmacol.* 2018;11(11):1113–1121.

Rivkees SA. Pediatric Graves' disease: management in the post-propylthiouracil era. *Int J Pediatr Endocrinol.* 2014;2014(1):10.

130. Has radioactive iodide fallen into disfavor as a treatment option for Graves disease?

On the contrary, radioactive iodide (^{131}I) is increasing in popularity. In some pediatric endocrinology centers, this is now considered the first line of therapy. Concern had been voiced about the possible risk for thyroid carcinoma, leukemia, thyroid nodules, or genetic mutations, but as the individuals treated with ^{131}I during childhood have been followed for prolonged periods, experience suggests that children are not at a significantly increased risk for developing these conditions.

Rivkees SA. Pediatric Graves' disease: management in the post-propylthiouracil era. *Int J Pediatr Endocrinol.* 2014;2014(1):10.

131. During a routine physical examination, a solitary thyroid nodule is palpated on an asymptomatic 10-year-old child. Can a wait-and-see approach be taken?

Absolutely not. In children with a solitary nodule, about 20% to 25% have a carcinoma; 20% to 30% have an adenoma; and the remainder will have thyroid abscess, thyroid cyst, multinodular goiter, Hashimoto thyroiditis, subacute thyroiditis, or nonthyroidal neck mass. Given the relatively high incidence of carcinoma, a thyroidal mass demands prompt evaluation. Previous irradiation to the head or neck is associated with a significantly increased incidence of thyroid carcinoma. A family history of thyroid disease increases the likelihood of chronic lymphocytic thyroiditis or Graves disease. The presence of tenderness on palpation or high titers of antithyroid antibodies points away from a malignant process. However, in all cases, radiologic studies should be undertaken; in many cases, surgical exploration is required.

132. How should this solitary thyroid nodule be investigated?

The principal tools used in the investigation of a thyroid mass include **^{123}I scanning** and **ultrasound**. Ultrasound is useful for delineating the size of the mass, its anatomic relationship to the rest of the thyroid, and the presence of cystic structures. ^{123}I imaging that reveals a single nonfunctioning (i.e., reduced uptake on scintiscan) mass ("cold" nodule) suggests a carcinoma or adenoma and is a clear indication for surgery. Patchy uptake is more characteristic of chronic lymphocytic thyroiditis, whereas a poorly functioning lobe may be found in a subacute thyroiditis. Fine-needle aspiration or biopsy is another approach to the investigation of a thyroid mass with current recommendations for aspiration of thyroid nodules ≥ 1 cm using ultrasound guidance.

Francis G, Waguespack SG, Bauer AJ, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2015;25(7):716–759.

Gupta A, Ly S. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. *J Clin Endocrinol Metab.* 2013;98(8):3238–3245.

133. What should be included in the differential diagnosis for low TSH and low thyroxine levels, particularly in a child with acute illness?

Although central hypothyroidism will result in both low TSH and thyroxine levels, in the acutely ill child one should consider **euthyroid sick syndrome** as the diagnosis. This is an adaptive response to lower metabolism in critical illness. Other findings include low serum T_3 levels and increased reverse T_3, a metabolically inactive metabolite. This picture may be complicated in the sick preterm infant as T_4, T_3, and free T_4 levels are generally lower. As the primary illness resolves, levels generally return to normal.

Marks SD. Nonthyroidal illness syndrome in children. *Endocrine.* 2009;36(3):355–367.

KEY POINTS: THYROID DISORDERS

1. Midline neck masses usually involve the thyroid gland or thyroid remnants, such as a thyroglossal duct cyst.
2. Neck extension improves visualization and palpation of thyroid masses, especially with swallowing.
3. About 20% to 25% of solitary thyroid nodules in adolescents are malignant; expedited evaluation is needed.
4. Chronic lymphocytic thyroiditis is the most common cause of pediatric goiter in the United States.
5. Chronic lymphocytic thyroiditis most commonly appears as an asymptomatic goiter, thereby reinforcing the need for thyroid palpation (an often-overlooked examination feature).
6. The best initial screening studies for hypothyroidism and hyperthyroidism are total T_4 and TSH.

Acknowledgment

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GASTROENTEROLOGY

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CLINICAL ISSUES

1. What is the definition of failure to thrive?

Failure to thrive (FTT) is a sign, not a diagnosis, and not a syndrome. It is a nonspecific term that describes either weight loss or poor weight gain and in many clinical settings is being replaced by the term *malnutrition*. In severe cases linear growth and head circumference can be affected. Some specific FTT growth chart–based definitions for children <2 years of age include (1) weight below the third and fifth percentile for age on more than one occasion, (2) weight declines two or more major percentile lines, (3) weight <80% of the ideal weight for age, and (4) a child below the third or fifth percentile on the weight-for-length curve. Z-scores can also be used to describe deviation from the mean, and Z-scores less than −2 (2 standard deviations) with regard to weight-for-age, weight-for length, or length-for-age may indicate abnormal growth.

Larson-Nath C, Bilank VF. Clinical review of failure to thrive in pediatric patients. *Pediatr Ann.* 2016;45(2):e46–e49.
Jaffe AC. Failure to thrive: current clinical concepts. *Pediatr Rev.* 2011;32(3):100-107.

2. What is the differential diagnosis of FTT?

It is useful to consider the following physiologic categories in the differential diagnosis of FTT:

- **Inadequate nutritional intake**: not enough food offered, child not taking in enough, excessive juice or milk, formula dilution
- **Malabsorption/loss**: gastrointestinal (GI) mucosal disease, pancreatic dysfunction, cholestatic liver disease, persistent vomiting, disaccharidase deficiency, protein-losing enteropathy
- **Increased metabolic demand**: congenital heart disease, chronic lung disease, chronic renal failure, acidosis, congenital or chronic infections, chronic systemic disease, genetic syndromes

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Jaffe AC. Failure to thrive: current clinical concepts. *Pediatr Rev.* 2011;32(3):100–107.

3. How is FTT evaluated?

The most important aspect of the evaluation for FTT is the history and physical examination, including growth curve. History should address feeding, stooling, developmental, psychosocial, and family history. The examination should also focus on any findings that suggest a malformation. Diagnostic testing is rarely useful, but may include a complete blood count (CBC), comprehensive metabolic profile (CMP), thyroid function studies, urinalysis, urine culture, and lead level.

4. How is the diagnosis of "pinworms" made?

Direct visualization of larger adult worms in the perianal region of a child can sometimes be successful, with the best examination time 2 to 3 hours after the child is asleep. Additionally, **transparent adhesive tape** can be applied to the perianal region to collect eggs; the tape can be examined under low-power microscopy (Fig. 7.1).

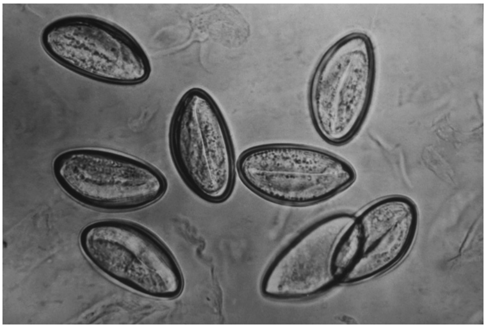

Fig. 7.1 Pinworm eggs as collected on adhesive tape. (From the Public Health Image Library, Centers for Disease Control and Prevention: http://phil.cdc.gov.)

These specimens are best obtained in the morning. Because few pinworm ova are present in stool, examination of stool specimens for ova and parasites (for pinworms) is not recommended.

American Academy of Pediatrics. Pinworm infection. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *2018 Red Book: Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:634–635.

5. What is intractable singultus?

Persistent hiccups. Hiccups result from involuntary, spasmodic contracture of the diaphragm accompanied by a sudden closure of the glottis. Persistent hiccups can be a diagnostic and therapeutic challenge with a broad differential diagnosis, including some central nervous system (CNS) possibilities, such as seizures and tumors.

Rouse S, Wodziak M. Intractable hiccups. *Curr Neurol Neurosci Rep.* 2018;18(8):51.

Chang FY, Lu CL. Hiccup: mystery, nature and treatment. *J Neurogastroenterol Motil.* 2012;18(2):123–130.

6. What is the most commonly ingested foreign body?

Coins account for more than 20,000 visits yearly to emergency departments (EDs) in the United States. Symptomatic patients are more likely to have the coin lodged in the esophagus, although a significant portion of these patients may be asymptomatic. Coins lodged in the esophagus should be removed endoscopically within 24 hours because of the risk for ulceration and perforation.

7. Which is potentially more dangerous after ingestion: a penny made in 1977 or one made in 1987?

The penny from 1987. In 1982, the composition of pennies changed. Coins minted after that date have higher concentrations of zinc, which is more corrosive and can be absorbed, potentially causing toxicity.

Dhawan SS, Ryder, KM, Pritchard, E. Massive penny ingestion: the loot with local and systemic effects. *J Emer Med.* 2008;35(1):33–37.

8. What is the difference radiographically between a coin in the esophagus and a coin in the trachea?

A coin in the esophagus appears *en face* in the anteroposterior view (sagittal plane), whereas a coin in the trachea appears *en face* in the lateral view (coronal plane) (Fig. 7.2). This occurs because the cartilaginous ring of the trachea is open posteriorly, but the opening of the esophagus is widest in the transverse position.

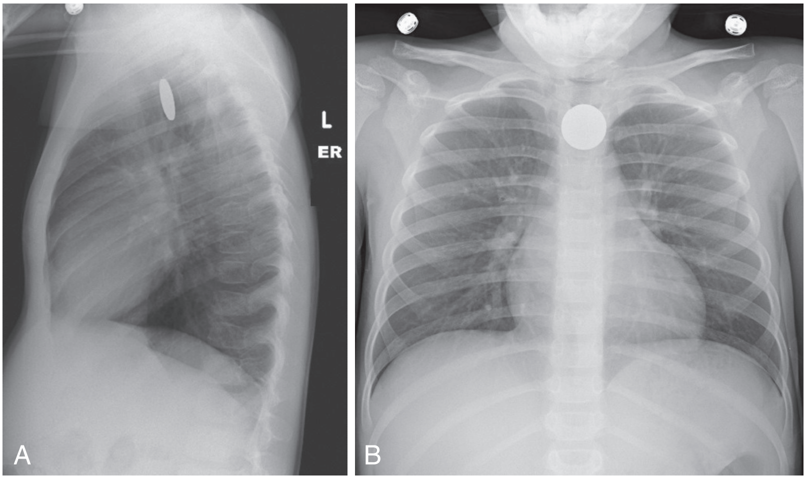

Fig. 7.2 Lateral (A) and anteroposterior (B) chest x-rays of a child show the ingested coin in the proximal esophagus. (From Ginsberg CG, Gostout CJ, Kochman M, Norton ID, eds. *Clinical Gastrointestinal Endoscopy*. 4th ed. Philadelphia, PA: Saunders/Elsevier; 2012:231.)

9. Why is ingestion of a button battery more dangerous than ingestion of a coin?

Button batteries, like coins, often become lodged in the esophagus. If this happens, they are capable of causing significant mucosal burns (sometimes in a matter of hours). In severe cases, batteries can erode through the wall of the esophagus and into surrounding structures, including the aorta. This can lead to fatal hemorrhage. For this reason, if there is *any* suspicion that there is a button battery stuck in the esophagus, it must be removed emergently. Ingesting honey or Carafate after swallowing a button battery may reduce the potential for injury and has been recommended by the National Poison Control Center, but is not a substitute for emergency care and appropriate endoscopic removal. Button batteries that reach the stomach do not pose as much risk, but should be followed to ensure passage and removed if they do not pass out of the stomach within 2 to 3 days. It is also always important to determine the type of button battery ingested.

National Poison Control Center. www.poison.org/battery/guideline. Accessed January 20, 2020.
Leinwand K, Brumbaugh DE, Kramer RE. Button battery ingestion in children. *Gastrointest Endosc Clin N Am.* 2016;26(1):99–118.

10. Which is more dangerous, two magnets that are swallowed together or two magnets that are swallowed separately?

Although swallowed magnets in any form always pose a significant risk, magnets that are swallowed **separately** pose greater risk. Magnets swallowed together usually attract (stick together), whereas magnets swallowed separately have the potential to migrate down the bowel separately and subsequently stick to each other across loops of bowel, leading to ischemia and possible perforation.

Sola R Jr, Rosenfield EH, Yu YR, et al. Magnet foreign body ingestion: rare occurrence but big consequences. *J Pediatr Surg.* 2018; 53(9):1815–1819.
Hussain SZ, Bousvaros A, Gilger M, et al. Management of ingested magnets in children. *J Pediatr Gastroenterol Nutr.* 2012;55(3): 239–242.

11. What are the indications for emergent foreign body removal?

In general, any object(s) swallowed that may be "stuck in the esophagus" based on symptoms (chest pain, odynophagia, dysphagia, epigastric pain, drooling, etc.), such as meat impactions, should be removed. Most sharp objects in the stomach should be emergently removed. Objects $>$2.5 cm wide and 5 cm long are unlikely to pass through the pylorus and should be removed. Patients who report *any* symptoms (e.g., vomiting, pain, fever, dysphagia) need emergent evaluation even if the object is in the stomach or intestine.

Kramer RE, Lerner DG, Lin T, et al. Management of ingested foreign bodies in children: a clinical report of the NASPGHAN Endoscopy Committee. *J Pediatr Gastroenterol Nutr.* 2015;60(4):562–574.

12. What is the grim news about Rapunzel syndrome?

Rapunzel syndrome, which results from trichotillomania, is a trichobezoar (a bezoar formed from hair) that can form a cast outline of the stomach and small intestine and over time may extend into the small bowel. **Surgical removal** is usually the only therapeutic option for removing large trichobezoars such as those seen in Rapunzel syndrome.

Laith S, Gopalakrishman KL, Ilangovan G, Jayajothi A. Rapunzel syndrome. *J Clin Diagn Res.* 2017;11(9):TD01–TD02.
Gonuguntla V, Joshi D-D. Rapunzel syndrome: a comprehensive review of an unusual case of trichobezoar. *Clin Med Res.* 2009; 7(3):99–102.

CONSTIPATION

13. What constitutes constipation in childhood?

Constipation is defined as a delay or difficulty in defecation present for 2 or more weeks and sufficient to cause distress in the patient. Normal stool frequency depends on the age of the child and varies from several times a day to three stools per week. In children, constipation should be considered when the normal stooling pattern becomes more infrequent, when stools become hard or are difficult to expel, or when the child exhibits withholding patterns or behavioral changes toward moving his or her bowels. Soiling (encopresis) can be a sign of constipation.

Mandani S, Tsang L, Kamat D. Constipation in children: a review. *Pediatr Ann.* 2016;45(5):e189–196.
Auth MKH, Vora R, Farrelly P, et al. Childhood constipation. *BMJ.* 2012;345:e7609.

14. What features suggest an organic etiology for constipation?

- Delayed passage of meconium beyond the first 24 hours of life
- History of weight loss or inadequate weight gain
- Lumbosacral nevi or sinus
- Multiple café au lait spots
- Abnormal neurologic examination (decreased tone, strength; abnormal reflexes)

- Anal abnormalities (anteriorly displaced, patulous, or tight)
- Gross or occult blood in stool
- Abdominal distention with or without vomiting

Lu P, Mousa HM. Constipation: beyond the old paradigms. *Gastroenterol Clin North Am*. 2018;47(4):845–862.
Croffie JM, Fitzgerald JF. Constipation and irritable bowel syndrome. In Liacouras CA, Piccoli DA, eds. *Pediatric Gastroenterology: The Requisites in Pediatrics*. Philadelphia, PA: Mosby Elsevier; 2008:33.

15. What is an important component of the physical examination when evaluating constipation?

The rectal examination. The presence of large amounts of stool in the rectal vault almost always indicates functional constipation. Lack of stool in the rectal vault could indicate recent evacuation. If expulsion of stool occurs after removal of the examining finger, Hirschsprung disease should be considered. The rectal examination in some children may be anxiety-provoking and uncomfortable, but steps can be taken to encourage cooperation in most children. Failure to perform a rectal examination is a common omission during the evaluation of children, and impaction in chronic constipation often goes undetected, though deferring or postponing the rectal examination in some children may be appropriate.

Orenstein SR, Wald A. Pediatric rectal exam: why, when, and how. *Curr Gastroenterol Rep*. 2016;18(1):4.

16. What are some common triggers of constipation in healthy infants and children?

- **Introduction of solid foods or cow milk**: Diet may be low in fiber and not provide adequate fluid intake.
- **Inadequate toilet training**: Toddlers may not respond appropriately to the need to defecate or may not have adequate foot support needed for effective evacuation of stool if using an adult-sized toilet. If passage of stool is painful, toddlers can begin to withhold stool. If stool is not made softer by increasing fiber and/or fluids in the diet or by stool softeners, this pattern can continue.
- **School entry:** Children may be reluctant to use the toilet at school, leading to a pattern of stool withholding, painful stools, and constipation.

Borowitz SM, Cox DJ, Tam A, et al. Precipitants of constipation during early childhood. *J Am Board Fam Pract*. 2013;16(3):213–218.

KEY POINTS: CONSTIPATION

1. Ninety-nine percent of full-term infants pass stool less than 24 hours after birth. Failure to pass stool within the first 48 hours of life should be considered pathologic until proved otherwise.
2. The rectal examination is a common omission among patients undergoing an evaluation for constipation. Tone, the amount of stool, and the size of the rectal vault should be assessed.
3. Fecal soiling is almost always associated with severe functional constipation and not Hirschsprung disease.
4. Treatment of functional constipation is multimodal and includes medications.
5. Organic causes are suggested by weight loss, lumbosacral nevi, anal abnormalities, blood in stool, and abdominal distention.

17. Which clinical features differentiate chronic retentive constipation from Hirschsprung disease?

See Table 7.1.

Table 7.1 Clinical Distinctions Between Chronic Retentive Constipation and Hirschsprung Disease

CLINICAL FEATURE	FUNCTIONAL CONSTIPATION	HIRSCHSPRUNG DISEASE
Age of onset	>1 yr	<1 yr
Passage of meconium	Within 24 hr	Beyond first 24 hr of life
Abdominal pain	Frequent, colicky	Rare
Stool size	Large	Small, ribbon-like
Stool withholding behavior	Present	Absent
Encopresis (soiling)	Present	Very rare
Rectum	Filled with stool	Empty
Rectal examination	Stool in rectum	Explosive passage of stool
Growth	Normal	Poor

18. How is Hirschsprung disease diagnosed?

Hirschsprung disease results from the failure of normal migration of ganglion cell precursors to their location in the GI tract during gestation. The diagnosis can be made by obtaining an unprepped **barium enema**, which will demonstrate a change in the caliber of the large intestine at the site where normal bowel meets aganglionic bowel (transition zone) (Fig. 7.3). An unprepped barium enema is required because the use of cleansing enemas can dilate the abnormal portion of the colon and remove some of the distal impaction, thereby resulting in a false-negative result. After the study, the retention of barium for 24 or more hours is suggestive of Hirschsprung disease or a significant motility disorder. This study is less reliable in a child younger than 6 months. **Rectal suction biopsies** or **full-thickness surgical biopsies** will confirm the absence of ganglion cells. **Anorectal manometry** is a motility test that can also be used in the evaluation of Hirschsprung disease. This test evaluates the rectoanal inhibitory reflex (RAIR). The RAIR consists of a reflex relaxation of the internal anal sphincter and transient contraction of the external anal sphincter when stool distends the rectum. The RAIR is absent in Hirschsprung disease (as well as in anal achalasia). Anorectal manometry is less reliable in children; in small infants, it requires specialized equipment and typically sedation or general anesthesia.

Rodriguez L, Nurko S. Gastrointestinal motility procedures. In Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal and Liver Disease.* 4th ed. Philadelphia, PA: Elsevier Saunders; 2011:696.

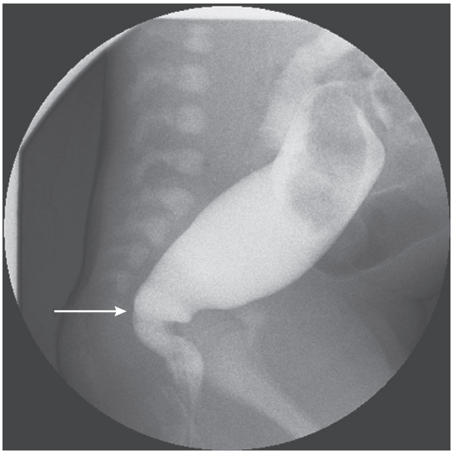

Fig. 7.3 Contrast enema in a newborn with Hirschsprung disease. Note the transition zone *(arrow)* as the more dilated proximal colon tapers to a narrower distal colon at the rectosigmoid junction. (From Liacouras CA, Piccoli DA. *Pediatric Gastroenterology: The Requisites in Pediatrics*. Philadelphia, PA: Elsevier Mosby; 2005:1170.)

19. What is the most common cause of encopresis?

Encopresis, or fecal soiling, may be defined as the involuntary passage of fecal material in an otherwise healthy and normal child. The most common cause is **functional constipation with overflow incontinence.** Children with encopresis typically sense no urge to defecate. Fecal soiling is almost always associated with severe functional constipation, which over time can lead to altered defecation dynamics.

20. How should children with chronic constipation and encopresis be managed?

- The rectosigmoid colon should be **aggressively cleansed** of fecal material. Manual disimpaction is sometimes required. Multiple enemas over multiple days are commonly needed. Adult enemas should be used in children who are older than 3 years.
- Medications that act as an **osmotic laxative** by drawing fluid into the intestine to promote the passage of soft stools include polyethylene glycol powder and lactulose (a nonabsorbable sugar). Other osmotic agents, such as sorbitol and magnesium citrate, can be considered. For cases of long-standing functional constipation, osmotic laxatives should be continued for a minimum of several months while the dilated rectum returns to normal size.
- An **oral lubricant**, such as mineral oil, can help promote the continued passage of stool but can contribute to accidental soiling. In difficult cases, oral **stimulant medications**, such as bisacodyl or senna, can be substituted for short-term use or longer term under the supervision of a pediatric gastroenterologist. Oral laxatives and stimulant medications are commonly used in conjunction.
- It is extremely important to **educate** patients and parents about the mechanics of the disorder. A diet with adequate fiber content, possible limitation of dairy and complex carbohydrates, defined periods of toilet sitting (two to three times daily for 10 minutes after meals), and a behavior modification system that rewards normal bowel movements are essential for eventual success. Integrative approaches of biofeedback, relaxation

strategies, and mental imagery have been used for children who have severe "defecation anxiety." A goal is one to two soft bowel movements per day. Relapses are common.

Colombo JM, Wassom MC, Rosen JM. Constipation and encopresis in childhood. *Pediatr Rev.* 2015;36(9):392–401.

DIARRHEA

21. How is diarrhea defined?

The World Health Organization defines diarrhea as the evacuation of at least three watery stools per 24-hour period. *Acute* diarrhea is often self-limiting and lasts for a few days. Diarrhea is considered *chronic* when lasting >14 days.

Feizizadeh S, Salehi-Abargouei A, Akbari V. Efficacy and safety of *Saccharomyces boulardii* for acute diarrhea. *Pediatrics.* 2014;134(1):e176-e191.

22. What is the most common cause worldwide of epidemic diarrhea?

Norovirus. These single-stranded RNA viruses are believed to be responsible for at least 50% of all gastroenteritis outbreaks worldwide and a major cause of foodborne illness. With the widespread use of rotavirus vaccination, norovirus has become the most common cause of medically attended acute gastroenteritis in children <5 years in the United States.

O'Brien SJ, Sanderson RA, Rushton SP. Control of norovirus infection. *Curr Opin Gastroenterol.* 2019;35(1):14-19.
Payne DC, Vinjé J, Szilagyi PG, et al. Norovirus and medically-attended gastroenteritis in the U.S. children. *N Engl J Med.* 2013;368:1121–1130.

23. What are other common causes of acute diarrhea?

- Viral (others include rotavirus, enterovirus)
- Food poisoning
- Bacterial (e.g., *Escherichia coli, Shigella, Salmonella, Yersinia, Campylobacter, Clostridioides difficile*)
- Protozoal/parasitic
- Allergic
- Medication side effect (e.g., antibiotic usage)
- Extraintestinal infections (e.g., respiratory, urinary, sepsis)

24. Which historical factors are key when seeking the cause of diarrhea?

- Associated symptoms, including changes in weight or growth, fevers, sweating, and palpitations
- Illnesses in other family members or close contacts
- Recent medication changes, especially antibiotics
- History of immunosuppression (e.g., recurrent major infections, history of malnutrition, acquired immunodeficiency syndrome, immunosuppressive medications)
- Family history of celiac disease or inflammatory bowel disease
- Travel outside of the United States
- Travel to or camping in rural or seacoast areas (i.e., involving the consumption of untreated water, raw milk, or raw shellfish)
- Attendance in day care
- Dietary history with particular focus on juice and fructose consumption
- Presence of family pets
- Exposure to recreational water (e.g., pools, water playgrounds)
- Food preparation and water source

Thielman NM, Guerrant RL. Acute infectious diarrhea. *N Engl J Med.* 2004;350(1):38–47.

25. Why is true diarrhea during the first few days of life especially concerning?

In addition to the greater potential for dehydration in a newborn, diarrhea in this age group is more commonly associated with major congenital intestinal defects involving electrolyte transport (e.g., congenital sodium- or chloride-losing diarrhea), carbohydrate absorption (e.g., congenital lactase deficiency), immune-mediated defects (e.g., autoimmune enteropathy), or epithelial barrier defects, including those characterized by villous blunting (e.g., microvillus inclusion disease). Many of these are monogenic disorders and together are referred to as **congenital diarrhea and enteropathies** (CODEs). Although viral enteritis can occur in the nursery, any newborn with true diarrhea warrants thorough evaluation and consideration for referral to a tertiary center.

Thiagarajah J, Kamin DS, Acra S, et al. Advances in evaluation of chronic diarrhea in infants. *Gastroenterology.* 2018;154(8):2045–2059.

26. What is the primary pathophysiologic difference between secretory and osmotic diarrhea?

In *osmotic diarrhea,* undigested nutrients increase the osmotic load in the distal small intestine and the colon, leading to decreased water absorption. In *secretory diarrhea,* a noxious agent causes the intestinal epithelium to secrete excessive water and electrolytes into the lumen.

27. How can osmotic diarrhea be distinguished from secretory diarrhea?

In true osmotic diarrhea, symptoms should cease when the patient is made NPO (nothing by mouth). In addition, a **fecal osmotic gap** can be calculated. In osmotic diarrhea, the fecal electrolyte content becomes lower than the serum. Stool electrolytes should be collected and compared with a normal serum osmolality: 290 mOsm/kg. The fecal osmotic gap is calculated by $[290 - 2(Na + K)]$.

See Table 7.2.

Table 7.2 Osmotic Diarrhea Versus Secretory Diarrhea

STOOLS	OSMOTIC DIARRHEA	SECRETORY DIARRHEA
Electrolytes	Na^+ <70 mmol/L	Na^+ >70 mmol/L
	Cl^- <25 mEq/L	Cl^- >40 mEq/L
Osmotic gap*	>135 mOsm	<50 mOsm
pH	<5.6	>6.0
Response to fasting	Improvement	None

*The osmotic gap is the osmolality of the fecal fluid minus the sum of the concentrations of the fecal electrolytes.

From Guarino A, DeMarco G. Persistent diarrhea. In Walker WA, Goulet O, Kleinman RE, et al, eds. *Pediatric Gastrointestinal Disease.* 4th ed. Hamilton, Ontario: B.C. Decker; 2004:180–193.

28. How should children with secretory diarrhea be managed?

Enteral nutrition should be withheld and fluid and electrolyte balance should be restored and maintained. The child should be evaluated for proximal small bowel damage with endoscopy, enteric pathogens, and a baseline malabsorption workup. If abnormalities of the mucosal integrity are suspected, a small bowel biopsy should be performed, and electron microscopy on such biopsies should be considered to evaluate for microvillus inclusion disease and cell structure anomalies; if the findings are significantly abnormal, the patient may be given parenteral alimentation and gradual refeeding. Electron microscopy may reveal congenital abnormalities of the microvillus membrane and the brush border. Hormonal causes of secretory diarrhea (e.g., a VIPoma, hypergastrinoma, or carcinoid syndrome) must be considered if initial studies are negative.

29. What rare tumors can cause true secretory diarrhea?

- **Gastrinoma**: Children typically present with ulcer pain, hematemesis, vomiting, and melena. High acid output into the proximal small bowel leads to precipitation of bile salts and steatorrhea.
- **VIPoma:** Children present with profuse, watery diarrhea with marked fecal losses (20 to 50 mL/kg/day) due to high levels of vasoactive intestinal peptide (VIP).

30. What features characterize "toddler diarrhea"?

Toddler diarrhea, which is also known as *chronic nonspecific diarrhea,* is a clinical entity of unclear etiology that occurs in infants between 6 and 40 months of age, often after a distinct identifiable enteritis and treatment with an antibiotic. Loose, nonbloody stools (at least two per day but usually more) occur without associated symptoms of fever, pain, or growth failure. Malabsorption is not a key feature.

There may be multiple pathophysiologies: overconsumption of fruit juices, relative intestinal hypermotility, increased secretion of bile acids and sodium, and intestinal prostaglandin abnormalities. While normal growth is always reassuring, a differential diagnosis, including disaccharide intolerance, food protein hypersensitivity, parasitic infection, celiac disease, and inflammatory bowel disease, should be considered. Treatment consists of reassurance, careful growth assessment, and psyllium bulking agents (as initial therapy). Other agents used with success have been cholestyramine and metronidazole.

Powell C, Jenkins H. Toddler diarrhea: is it a useful diagnostic label? *Arch Dis Child.* 2012;97:84–86.

31. How do various oral rehydration solutions differ in composition from other liquids that are commonly used for rehydration?

Many home remedies are either very deficient or very excessive in electrolytes or sugar. Chicken broth has no carbohydrates and very high sodium. Sodas (such as cola) can have up to eight times the recommended sugar content with negligible sodium and potassium. Apple juice has very high sugar content and very high osmolality and negligible sodium. Tea has neither carbohydrate nor sodium. Commercially available oral rehydration solutions incorporate carbohydrates (25 to 50 g/L), sodium (45 to 90 mEq/L), and potassium (20 to 25 mEq/L) to maximize coupled transport.

32. How can the World Health Organization's (WHO) oral electrolyte (rehydration) solution be duplicated?

The WHO solution is 2% glucose, 20 mEq K^+/L, 90 mEq Na^+/L, 80 mEq Cl^-/L, and 30 mEq bicarbonate/L. This solution is approximated by adding ¾ tsp of salt, 1 tsp of baking soda, 1 cup of orange juice (for KCl), and 8 tsp of sugar to 1 L of water.

33. What traditional approaches to feeding during diarrhea are no longer recommended and should be avoided?

- **Switching to lactose-free formula:** This is usually unnecessary because, for most infants, clinical trials have not shown an advantage. Certain infants with severe malnutrition and dehydration may benefit from lactose-free formula.
- **Diluted formula:** Half- or quarter-strength formula has been shown in clinical trials to be unnecessary and associated with prolonged symptoms and delays in nutritional recovery.
- **Clear liquids**: Foods high in simple sugars (e.g., carbonated soft drinks, juice drinks, gelatin desserts) should be avoided because the high osmotic load might worsen diarrhea.
- **Avoid fatty foods:** Fat may have a beneficial effect of reducing intestinal motility.
- **BRAT diet:** The **b**ananas, **r**ice, **a**pplesauce, and **t**oast diet is unnecessarily restrictive and can provide suboptimal nutrition.
- **Avoid food for at least 24 hours:** Early feeding decreases the intestinal permeability caused by infection, reduces illness duration, and improves nutritional outcome.

King CK, Glass R, Bresee JS, Duggan C, Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep.* 2003;52:1–16.

34. What is the role of antiemetic agents in children with gastroenteritis?

Oral ondansetron, a centrally acting 5-hydroxytryptamine antagonist, has been found to be useful in decreasing the risk for persistent vomiting, lessening the need for intravenous therapy in ED settings and reducing the likelihood of hospitalization. Other antiemetic medications, particularly domperidone, metoclopramide, prochlorperazine, and promethazine, have not been recommended because of concerns of increased ED visits, increased rates of misdiagnoses requiring ED revisitation, and increased health care costs.

Romano C, Dipasquale V, Scarpignato C. Antiemetic drug use in children: what the clinician needs to know. *J Pediatr Gastroenterol Nutr.* 2019;68(4):466–471.

Freedman SB, Hall M, Shah SS, et al. Impact of increasing ondansetron use on clinical outcomes in children with gastroenteritis. *JAMA Pediatr.* 2014;168(4):321–329.

35. What are nonantimicrobial drug therapies for diarrhea?

In older children, adolescents, and adults, the following categories are used. Pediatric data are limited, and these medications are not typically approved or recommended for children <3 years of age.

- **Antimotility agents** (loperamide [Imodium], diphenoxylate and atropine [Lomotil], tincture of opium [Paregoric]): These can cause drowsiness, ileus, and nausea and potentiate the effects of certain bacterial enteritides (e.g., *Shigella*, *Salmonella*) or accelerate the course of antibiotic-associated colitis.
- **Antisecretory drugs** (bismuth subsalicylate [Pepto-Bismol]): These medications have the potential for salicylate overdose.
- **Adsorbents** (attapulgite, kaolin-pectin [Donnagel, Kaopectate]): These can cause abdominal fullness and interfere with other medications.

36. What is the role of probiotic organisms in the treatment of antibiotic-associated diarrhea?

Probiotics (which are the opposite of antibiotics) are living organisms that are believed to cause health benefits by replenishing some of the more than 500 species of intestinal bacteria that antibiotics can suppress and by inhibiting the growth of more pathogenic flora. Among children receiving broad-spectrum antibiotics, about 20% to 40% are likely to experience some degree of diarrhea. *Lactobacillus GG*, *Bifidobacterium bifidum, Streptococcus thermophiles,* and *S. boulardii* have been shown to limit antibiotic-associated diarrhea in children.

Szajewska H, Canani RB, Guarino A, et al. Probiotics for the prevention of antibiotic-associated diarrhea in children. *J Pediatr Gastroenterol Nutr.* 2016;62(3):495–506.

37. Why is *Salmonella* enteritis so concerning in a child who is younger than 12 months?

In older children with *Salmonella* gastroenteritis, secondary bacteremia and dissemination of disease rarely occur. In infants, however, 5% to 40% may have positive blood cultures for *Salmonella,* and in 10% of these cases, *Salmonella* can cause meningitis, osteomyelitis, pericarditis, and pyelonephritis. Thus, in infants who are younger than 1 year, outpatient management of diarrhea assumes even greater significance, particularly if *Salmonella* is suspected.

38. What are the clinical manifestations of typhoid fever?

Typhoid fever is caused by *Salmonella* species *typhi* and *paratyphi*. It is characterized by fever, abdominal pain, nausea, decreased appetite, and constipation over the first week. The fever is sometimes paradoxically associated with bradycardia (Faget sign or sphygmothermic dissociation). Leukopenia is common. Diarrhea begins after approximately a week. If untreated, it can last for 2 to 3 weeks and cause significant weight loss and melena. Treatment of typhoid fever is necessary only in patients with sepsis or bacteremia with signs of systemic toxicity or a metastatic focus, which can include otitis, endocarditis, cholecystitis, or encephalitis.

39. Who was Typhoid Mary?

In 1907, a *JAMA* article traced a series of outbreaks of *Salmonella*-triggered typhoid fever in seven families over a 7-year period to the same cook, Mary Mallon, who had been employed by each family during that period. She was subsequently found to be a carrier of *Salmonella,* the first asymptomatic typhoid carrier identified in the United States. Much of the remainder of her life was spent in an imposed quarantine.

Marineli F, Tsoucalas G, Androutsos G. Mary Mallon (1869-1938) and the history of typhoid fever. *Ann Gastroenterol.* 2013;26(2):132–134.

40. What is the most common cause of travelers' diarrhea?

Enterotoxigenic *Escherichia coli* is the most commonly identified cause of travelers' diarrhea. Depending on the location, however, other bacteria (such as *Campylobacter* in Southeast Asia), viruses (norovirus, rotavirus), or parasites (*Giardia, Cryptosporidium*) can be present.

41. How can travelers' diarrhea be prevented?

- **Avoidance:** In high-risk areas of developing countries, avoid previously peeled raw fruits and vegetables and any foods or beverages or ice cubes prepared with tap water.
- **Bismuth subsalicylate:** Prophylactic bismuth subsalicylate (Pepto-Bismol) has been shown to minimize diarrheal illness in up to 75% of adults. Although some authorities recommend its use in children, others argue against it because of the risk for salicylate intoxication. It can interfere with the absorption of doxycycline used for malaria prevention.
- **Anti-infective drugs:** Prophylactic use of antimicrobial agents such as trimethoprim–sulfamethoxazole, azithromycin, neomycin, doxycycline, and fluoroquinolones can decrease the frequency of travelers' diarrhea in children and adults. However, routine use of antibiotics is not recommended because of potential risks for allergic drug reactions, antibiotic-associated colitis, and the development of resistant organisms.
- **Immunization:** Although potentially an ideal solution, at present it is not an alternative.

Steffen R, Hill Dr. DuPont HL. Traveler's diarrhea: a clinical review. *JAMA.* 2015;313(1):71–80.
Hill DR, Ryan ET. Management of travelers' diarrhea. *BMJ.* 2008;337:863–867.

42. Which bacterial gastroenteritides may benefit from antimicrobial therapy?

See Table 7.3.

Table 7.3 Benefits of Antimicrobial Therapy in Specific Bacterial Gastroenteritides

ENTEROPATHOGEN	INDICATION FOR OR EFFECT OF THERAPY
Shigella species	Shortens duration of diarrhea Eliminates organisms from feces
Campylobacter jejuni	Shortens duration Prevents relapse
Salmonella species	Indicated for infants <12 mo Bacteremia Metastatic foci (e.g., osteomyelitis) Enteric fever Immunocompromise
Escherichia coli	
Enteropathogenic	Use primarily in infants Intravenous use if invasive disease

Continued on following page

Table 7.3 Benefits of Antimicrobial Therapy in Specific Bacterial Gastroenteritides (*Continued*)

ENTEROPATHOGEN	INDICATION FOR OR EFFECT OF THERAPY
Enterotoxigenic (ETEC)	Most illnesses brief and self-limited
Enteroinvasive	Mimics shigellosis with diarrhea and high fever
Yersinia enterocolitica	None for gastroenteritis alone but indicated if suspected septicemia or other localized infection
Clostridioides difficile	10%-20% relapse rate

43. What strains of *Escherichia coli* are associated with diarrhea?

- **Enterotoxigenic** (ETEC): responsible for travelers' diarrhea
- **Enteropathogenic** (EPEC): similar mechanism as ETEC; adheres to epithelial cells and releases toxins that induce intestinal secretions and limit absorption; responsible for epidemics in day care settings and nurseries
- **Enteroinvasive** (EIEC): invades mucosa and causes bloody diarrhea
- **Enterohemorrhagic** (EHEC): produces a Shiga-like toxin that is responsible for hemorrhagic colitis; usually associated with contaminated food and undercooked beef; usually a self-limited gastroenteritis

44. What clinical entity has been attributed to EHEC, specifically strain O157:H7?

Hemolytic uremic syndrome (HUS), which is the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure.

45. What is the most common cause of antibiotic-associated colitis?

Clostridioides difficile, formerly Clostridium difficile (with a reclassification occurring in 2016). Fever, abdominal pain, and bloody diarrhea begin as early as a few days after starting antibiotics (especially clindamycin, ampicillin, and cephalosporins). Definitive diagnosis is made by sigmoidoscopy, which reveals pseudomembranous plaques or nodules (Fig. 7.4).

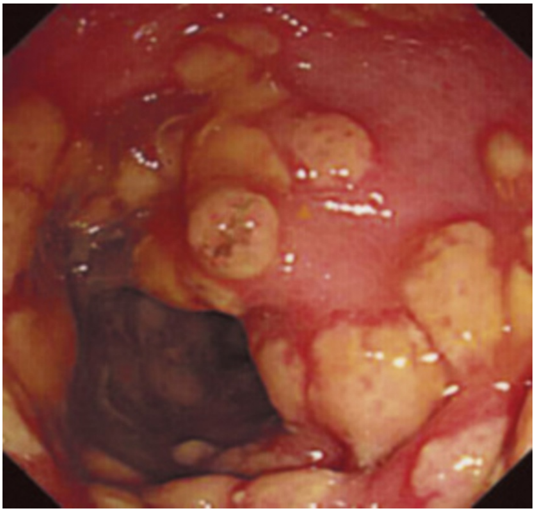

Fig. 7.4 Sigmoidoscopic appearance of pseudomembranes (whitish plaques) of *C. difficile* infection. (From Ralston SH, Penman ID, Strachan MWJ, Hobson RP, eds. *Davidson's Principles and Practice of Medicine*. 23rd ed. Edinburgh: Churchill Livingstone/Elsevier; 2018:270.)

46. How is the diagnosis of *C. difficile* made?

C. difficile causes diarrhea by producing two diarrheagenic toxins (A and B). Immunoassay for the toxins was previously the diagnostic test of choice. Since 2013, the American College of Gastroenterology has recommended that **nucleic acid amplification tests**, such as *polymerase chain reaction (PCR) assays*, which detect toxin-encoding genes, should be the standard diagnostic test because of superior sensitivity and specificity.

Guery B, Galperine T, Barbut F. *Clostridioides difficile:* diagnosis and treatment. *BMJ.* 2019;366:14609.

Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol.* 2013;108(4):478–498.

47. How common is asymptomatic *C. difficile* carriage?

Colonization rates in infants can be up to 70%, with percentages decreasing with age. By the second year of life, the rate declines to about 6%, and above age 2 years to 3%, which is the approximate rate in adults. These high colonization rates make the interpretation of positive tests in younger infants problematic. Toxin assays are more indicative of *C. difficile*–associated disease than culture. However, the toxin may be present without any symptoms, especially in infants, who typically do not have the toxin receptors necessary for disease. Unless there is evidence of histologic colitis, asymptomatic carriers do not require treatment.

Bryant K, McDonald LC. *Clostridium difficile* infections in children. *Pediatr Infect Dis J.* 2009;28(2):145–146.

48. Why are alcohol-based sanitizers insufficient when examining patients with *C. difficile?*

Typical alcohol-based hand hygiene products do not kill the spores of *C. difficile.* In addition to standard contact precautions (which include gloves at all times and gowns for direct contact with the patient or items in the room), handwashing with soap and water is recommended to more effectively remove spores from contaminated hands.

Kundrapa S, Sunkesula V, Jury I, et al. A randomized trial of soap and water hand wash versus alcohol hand rub for removal of *Clostridium difficile* spores from hands of patients. *Infect Control Hosp Epidemiol.* 2014;35(2):204–206.

49. When should a child be referred for a fecal transplant?

A *fecal microbiota transplant (FMT),* or *fecal bacteriotherapy,* is the infusion of feces (stool) from a healthy donor into a recipient via a colonoscopy. The only current indication for FMT is *Clostridioides difficile* infection. FMT should be considered in recurring or relapsing mild to moderate infection and failure of a prolonged (6 to 8 weeks) taper of vancomycin therapy or in the case of more severe infection, when there is little or no response to the initiation of vancomycin therapy.

Hourigan S, Oliva-Hemker M. Fecal microbiota transplantation in children: a brief review. *Pediatr Res.* 2016;80(1):2–6.

50. What are the three most common presenting symptoms of giardiasis?

- **Asymptomatic** carrier state
- **Chronic malabsorption** with steatorrhea and FTT
- **Acute gastroenteritis** with diarrhea, weight loss, abdominal cramps, abdominal distention, nausea, and vomiting

51. How reliable are the various diagnostic methods for detecting *Giardia*?

- Single stool examination for trophozoites or cysts: 50% to 75% (Fig. 7.5)

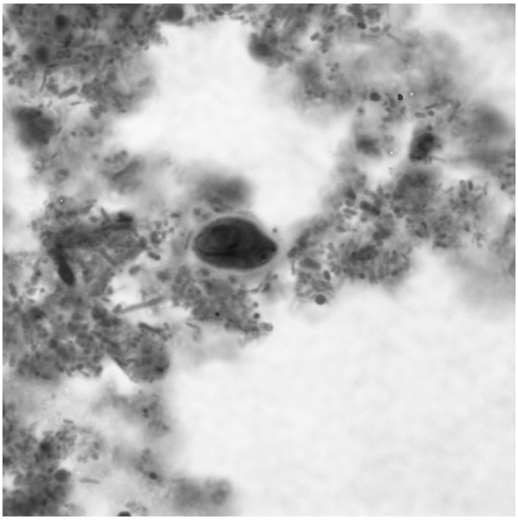

Fig. 7.5 Trichrome stain of stool revealing cystic form of *Giardia* (in center). (From Liacouras CA, Piccoli DA. *Pediatric Gastroenterology: The Requisites in Pediatrics*. Philadelphia, PA: Elsevier Mosby; 2005:7.)

- Three stool examinations (ideally 48 hours apart) for same: 95%
- Single stool examination and stool enzyme-linked immunosorbent assay test for *Giardia* antigen: >95%
- Duodenal aspirate or string test: >95%
- Duodenal biopsy (gold standard): closest to 100%

52. What are the potential complications of amebiasis?

The parasite *Entamoeba histolytica* disseminates from the intestine to the liver in up to 10% of patients and to other organs less commonly.

- Liver abscess
- Pericarditis
- Cerebral abscess
- Empyema

Haque R, Huston CD, Hughes M, et al. Amebiasis. *N Engl J Med.* 2003;348(16):1565–1573.

53. Why is *Cryptosporidium* such a problematic parasite?

Cryptosporidium, an intracellular protozoan parasite, causes profuse, watery diarrhea that can last up to 3 weeks in immunocompetent hosts and can cause life-threatening wasting in immunocompromised patients. It is more common in children than in adults. Fecal–oral transmission has multiple sources: ingestion of contaminated recreational or drinking water, contaminated food or liquids (e.g., unpasteurized milk or apple cider or cafeteria food), or contact with infected persons or animals (e.g., cattle). In the United States, outbreaks have been increasing by 13% per year since 2009. In particular, the parasite has features that make these outbreaks more difficult to prevent among children:

- Children shed higher levels of oocytes compared with adults.
- Even after a diarrheal illness ends, infectious oocytes can be excreted in the stool for up to 5 weeks, which facilitates day care and recreational pool contamination. (Centers for Disease Control and Prevention [CDC] recommendations are for no swimming in public pools by children for at least 2 weeks after resolution of a diarrheal illness.)
- Dogs and cats, plentiful as household pets, may serve as zoonotic reservoirs for human cryptosporidiosis.
- Oocytes of *Cryptosporidium* are extremely resistant to chemical disinfection, including chlorine used in pools.
- Oocytes can survive for months in surface water and soil.

Gharpure R, Perez A, Miller AD. Cryptosporidiosis outbreaks—United States, 2009-2017. *MMWR Morb Mortal Wkly Rep.* 2019; 68(25):568–572.

Rossie NF, Latif B. Cryptosporidiosis as threatening health problem: a review. *Asian Pac J Trop Biomed.* 2013;3(11):916–924.

ESOPHAGEAL DISORDERS

54. What underlying diagnoses should be considered in a patient who presents with a meat impaction in the esophagus?

- Eosinophilic esophagitis
- Achalasia
- Esophageal stricture, congenital or acquired
- Prior esophageal surgery

Of note, in children with esophageal food impaction, endoscopy and biopsy reveal an underlying pathologic and potentially treatable etiology in the majority of patients.

Hurtado CW, Furuta GT, Kramer RE. Etiology of food impactions in children. *J Pediatr Gastroenterol Nutr.* 2011;52(1):43–46.

55. A teenage girl has symptoms of swallowing difficulties, improved by positional head and neck changes, nocturnal regurgitation, and halitosis. What is the leading diagnosis?

Achalasia is a motor disorder of the esophagus characterized by loss of esophageal peristalsis, increased lower esophageal sphincter (LES) pressure, and absent or incomplete relaxation of LES with swallowing. Most cases are sporadic, and patients can present at any age from birth until the ninth decade of life. Suspected causes include autoimmune, infectious, and environmental triggers.

56. What are the key tests to diagnose achalasia?

A **barium swallow/video-esophagram** will show a variable degree of esophageal dilatation with tapering at the gastroesophageal junction. Fig. 7.6 shows the characteristic "bird's beak" esophagus. Later in the disease process, the proximal esophagus can become widely dilated and tortuous, and plain chest x-ray may show a widened mediastinum. **Esophageal manometry** (esophageal motility study) measures the pressure generated by the esophageal muscle. It can detect achalasia earlier in its course when a video-esophagram may be normal.

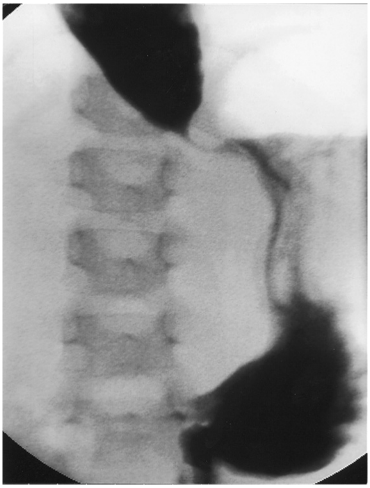

Fig. 7.6 Barium swallow in a child with achalasia showing esophageal dilation and rapid tapering in a beaklike appearance. (From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 3rd ed. Philadelphia, PA: Saunders; 2006:330.)

57. What are treatment options for achalasia?

Treatment options include **pneumatic dilations** (via therapeutic endoscopy), **peroral endoscopic myotomy** (POEM), **corrective laparoscopic surgery**, **botulinum toxin injection** at the LES, and **pharmacologic therapies**. Pneumatic dilation is relatively well tolerated, but it often needs to be repeated if symptoms recur. POEM allows for myotomy of abnormal circular fibers and preserving outer longitudinal esophageal muscle fibers without hiatal dissection. Regardless of treatment modality used, patients continue to be at increased risk for aspiration secondary to pooling of food and saliva in the esophagus after meals. Many have complications of reflux esophagitis, which require ongoing surveillance.

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van Lennep M, van Wijk MP, Omari TIM, et al. Clinical management of pediatric achalasia. *Expert Rev Gastroenterol Hepatol.* 2018; 12(4):391–404.

Kethman WC, Thorson CM, Sinclair TJ, et al. Initial experience with peroral endoscopic myotomy for treatment of achalasia in children. *J Pediatr Surg.* 2017;53(8):1532–1536.

58. What is the most common condition that might present as a food impaction in an *adolescent*?

Eosinophilic esophagitis (EoE). Occurring in children and adults, EoE is characterized by multiple symptoms that are suggestive of gastroesophageal reflux (GER), including heartburn, emesis, regurgitation, epigastric pain, and feeding difficulties, which are typically unresponsive to acid suppression therapy. Pathologically, this entity is characterized by eosinophilic inflammation of the esophagus and is almost always related to food antigens. In adolescents and adults, EoE often presents with symptoms of dysphagia or, occasionally, food impaction.

59. How is EoE diagnosed?

The diagnosis of EoE requires **upper endoscopy with biopsies**. According to the most recent EoE guidelines, EoE is a defined clinicopathologic diagnosis that consists of isolated esophageal dysfunction and esophageal biopsies with more than 15 eosinophils per high-power field. Other causes of an isolated esophageal eosinophilia must be excluded. Previously, adequate treatment with proton pump inhibition (PPI) for possible gastroesophageal reflux disease (GERD) before initial endoscopy had been considered a necessary diagnostic criterion to exclude the contribution of GER to the development of esophageal eosinophilia; however, the most recent international consensus classifies PPI as a treatment for EoE. It is no longer recommended to treat with PPI before the initial diagnostic endoscopy for EoE.

Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology.* 2018;155(4):1022–1033.e10.

60. What are common endoscopic findings in EoE?

- Esophageal furrowing and edema
- Esophageal rings, or “trachealization” (Fig. 7.7)
- White plaques
- Esophageal strictures
- Mucosal tearing

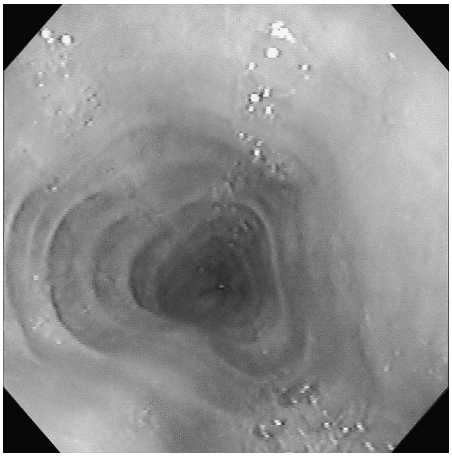

Fig. 7.7 "Trachealization" or "felinization" of the midesophagus of a patient with EoE. The terms arise from the ringed appearance of the esophagus that cause it to resemble a human trachea or a cat esophagus, which has rings of cartilage. (From Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal and Liver Disease*. 4th ed. Philadelphia, PA: Saunders; 2011:398.)

61. What causes esophageal eosinophilia in EoE?

EoE is an antigen-driven, immune-mediated disease. Although aeroallergens have been implicated, specifically in mouse models, the **ingestion of food antigens** is the primary driver of disease pathogenesis. A pathologic response induces a chronic inflammatory infiltrate in the esophagus with hyperplasia of the epithelia and muscular layers and fibrosis of the lamina propria.

Ruffner MA, Kennedy K, Cianferoni A. Pathophysiology of eosinophilic esophagitis: recent advances and their clinical implications. *Expert Rev Clin Immunol.* 2018;3:1–13.

62. What are the symptoms of EoE?

- *Infants/toddlers*: FTT, feeding issues, irritability, vomiting, regurgitation
- *Children*: epigastric abdominal pain, vomiting, regurgitation, heartburn, and other GERD symptoms, as well as dysphagia
- *Adolescents*: GERD symptoms, heartburn, dysphagia, and food impaction

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Ruffner MA, Spergel JM. Pediatric eosinophilic esophagitis: updates for the primary care setting. *Curr Opin Pediatr.* 2018;30(6):829–836.

Liacouras CA, Spergel J, Gober LM. Eosinophilic esophagitis: clinical presentation in children. *Gastroenterol Clin North Am.* 2014;43: 219–229.

63. What are the therapies for EoE?

- **Dietary restriction** involves the removal of the offending food antigen(s).
  - Elemental formula is greater than 98% effective at inducing and maintaining disease remission; however, poor palatability and cost provide some limitations.
  - A six-food elimination diet (removing dairy, wheat, eggs, soy, nuts, fish/shellfish) has been shown to improve symptoms and esophageal histology in 65% to 75% of patients. Foods may also be removed one at a time.
  - An allergy-directed diet using skin prick tests and atopy patch tests to determine offending foods has been shown to improve symptoms and esophageal histology in 60% to 70% of patients.
- **Topical swallowed steroids** (e.g., viscous budesonide, fluticasone metered dose inhaler [MDI]) are common pharmacologic medications used to treat EoE. These medications are used for both the initial treatment and for maintenance therapy.
- **Proton pump inhibitors** are utilized to reduce acid production in patients with GERD and may promote anti-inflammatory mechanisms.
- **Oral steroids** are used when severe symptoms are present and can promote immediate histologic and symptomatic recovery; however, they are not used long-term for maintenance therapy.

Munoz-Persy M, Lucendo AJ. Treatment of eosinophilic esophagitis in the pediatric patient: an evidence-based approach. *Eur J Pediatr.* 2018;177(5):649–663.

Dellon ES, Liacouras CA. Advances in clinical management of eosinophilic esophagitis. *Gastroenterology.* 2014;147(6):1238–1254.

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FOOD ALLERGIES

64. What are the most common food allergies in children?

Cow milk and **eggs** are the most common food allergies in children worldwide. In the United States, **peanuts** are the third most common. Soy, wheat (third in Germany and Japan), tree nuts (third in Spain), fish, and shellfish are also common allergens. Sesame is the third most common in Israel.

Longo G, Berti I, Burks AW, et al. IgE-mediated food allergy in children. *Lancet.* 2013;382(9905):1656–1664.
Food Allergy and Anaphylaxis Network. www.foodallergy.org. Accessed January 20, 2020.

65. How are adverse food reactions characterized?

- **Food allergy:** Ingestion of food results in hypersensitivity reactions mediated most commonly by immunoglobulin E (IgE).
- **Food intolerance:** Ingestion of food results in symptoms not immunologically mediated, and causes may include toxic contaminants (e.g., histamine in scombroid fish poisoning), pharmacologic properties of food (e.g., tyramine in aged cheeses), digestive and absorptive limitations of host (e.g., lactase deficiency), or idiosyncratic reactions.

Guandalini S, Newland C. Differentiating food allergies from food intolerances. *Curr Gastroenterol Rep.* 2011;13(5):426–434.

66. What can be acute manifestations of milk protein allergy in childhood?

- Angioedema
- Urticaria
- Acute vomiting and diarrhea
- Anaphylactic shock
- GI bleeding

67. What is the most common chronic manifestation of milk protein allergy?

Diarrhea of variable severity. Histologic abnormalities of the small intestinal mucosa have been documented, with the most severe form seen as a flat, villous lesion. Protein-losing enteropathy may result from disruption of the surface epithelium. The stools of children with primary milk protein intolerance often contain blood.

Warren CM, Jhaveri S, Warrier MR, et al. The epidemiology of milk allergy in US children. *Ann Allergy Asthma Immunol.* 2013;110(5):370–374.

68. What likely condition does a birch-allergic child have who develops tongue swelling when eating an apple?

Oral allergy syndrome, also called **pollen-food allergy syndrome**. In this IgE-mediated hypersensitivity condition, allergic children develop pruritus; tingling; and swelling of the lips, palate, and tongue when ingesting certain fresh fruits and vegetables because of cross-reactivity to proteins similar to those in pollen. In this case, birch shares allergens with raw carrots, celery, and apples. Symptoms generally are limited to the mouth but occasionally can progress to anaphylaxis. Most allergens are heat labile, so this patient should be advised to stick to baked apple pie for dessert.

Price A, Ramachandran S, Smith GP, et al. Oral allergy syndrome (pollen-food allergy syndrome). *Dermatitis.* 2015;26(2):78–88.

69. Should we feed infants allergenic foods as early as possible to prevent food allergies?

Two landmark randomized clinical trials have dramatically changed the consensus on “early” introduction of foods at 3 to 6 months of age. The Learning Early About Peanut (LEAP) trial demonstrated that introduction of *peanuts* at 4 months in infants developmentally ready for oral feeding reduced the rate of peanut allergy in infants with risk factors (severe atopic dermatitis or egg allergy). The American Academy of Pediatrics (AAP), together with several other professional societies, revised the guidelines to prevent peanut allergy in 2017, specifically outlining infants who would benefit most from early introduction. The prior guideline, which advised avoidance of peanuts in high-risk children until 3 years of age, has been rescinded. The Enquiring About Tolerance (EAT) study also provided evidence that introduction at 3 months of age of peanut, as well as egg, in breastfed infants appeared to lower the risk for later allergy to these specific foods. Time of introduction, however, had no impact on the development of allergy to cow milk, sesame, fish, or wheat. The lack of increased food allergy in “early” introduction, however, has led to the widespread acceptance of the introduction of foods to infants appropriate to their oral development, regardless of allergenic potential, and in line with family preferences.

Chan ES, Abrams EM, Hildebrand KJ, Watson W. Early introduction of foods to prevent food allergy. *Allergy Asthma Clin Immunol.* 2018;14(Suppl 2):57.
Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med.* 2016;374(18):1733–1743.
Du Troit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med.* 2015;372(9):803–813.

70. What are the symptoms of food protein–induced allergic proctocolitis or milk protein intolerance in an infant?

Infants, usually between birth and 4 months of age, develop frequent, mucus-streaked, bloody stools. Abdominal pain, irritability, and vomiting may be present. Poor weight gain is of particular concern and requires prompt treatment.

71. Does the diagnosis of food protein–induced allergic proctocolitis in infants usually require endoscopy?

No. The diagnosis is usually made based on **clinical history** and **physical examination** without the need for an endoscopy. Infants are typically being fed a milk-based formula or breast milk from a mother with a cow milk–based diet. Proctocolitis is treated by removing the offending food antigen (cow milk). Soy has high protein cross-reactivity with cow milk protein. Breastfeeding mothers should abstain from cow milk and soy. Sometimes additional foods need to be excluded. In formula-fed infants, switching to a soy-based formula is usually unsuccessful due to the protein cross-reactivity, so it is recommended to switch to a partially hydrolyzed protein formula. If symptoms persist, an amino acid–based formula may be necessary. It is important to counsel patients that it may take 3 to 6 weeks to see complete improvement in both clinical symptoms and GI bleeding.

Novak-Wegrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol.* 2015; 135(5):1114–1124.

FUNCTIONAL GASTROINTESTINAL DISORDERS

72. Rome wasn't built in a day, but what about the Rome criteria for functional gastrointestinal disorders (FGIDs)?

The *Rome criteria* involve systematic approaches to classify FGIDs. They have gone through four revisions, beginning with Rome I in 1989 to Rome IV in 2016. The Rome criteria, derived through a consensus (Delphi) process, are designed to categorize FGIDs. Because FGIDs by definition lack a structural basis to explain the findings, diagnostic categories are developed on the basis of epidemiology, pathophysiology, psychosocial, and symptom-based clinical features along with specific treatment modalities. Rome IV encompasses 33 adult and 17 pediatric FGIDs. Of note, the name derives from The Rome Foundation, a nonprofit organization that spearheaded consensus committees on these topics (the first was irritable bowel syndrome [IBS]) beginning in the late 1980s in—of course—Rome, Italy.

Drossman DA, Hasler WL. Rome IV-Functional GI disorders: disorders of gut-brain interaction. *Gastroenterology.* 2016;150(6): 1257–1261.

73. What characterizes FGIDs in children?

Functional abdominal pain (FAP), either recurrent or continuous, refers to pain that, after examination and testing, cannot be explained by a detectable abnormality. In Rome IV parlance, an FGID is diagnosed when "after appropriate medical evaluation the symptoms cannot be attributed to another medical condition." Thus there is no evidence of inflammatory, anatomic, infectious, allergic, metabolic, or neoplastic processes, although extensive diagnostic testing is not necessarily required. Pain should not occur solely during physiologic events (e.g., eating, menstrual periods) and must have been present for at least 2 months for at least four times per month. The cause of FAP is likely multifactorial, including genetic predisposition, complex interactions/dysregulation in the central and enteric nervous systems, altered gut signaling, contributions from ingested food, and perturbations of the intestinal microbiome. Abdominal pain may originate from visceral hyperalgesia or a decreased threshold for pain in response to changes in intraluminal pressure secondary to physiologic stimuli. Sensitizing psychosocial events (e.g., depression, anxiety, family stress, coping style, and abuse history) and sensitizing medical events (e.g., previous inflammation or distension) may also be factors.

Hyams JS, DiLorenzo C, Saps M, et al. Functional disorders: children and adolescents. *Gastroenterology.* 2016;150(6):1456–1468.

74. How common is chronic abdominal pain in children?

Very common. It is estimated that at some point 10% to 20% of children in the United States will experience chronic abdominal pain, defined as symptoms persisting >2 months. Chronic abdominal pain is also a common worldwide problem with FAP disorders estimated to affect about 12% to 15% of children.

Korterink JJ, Diederen K, Benninga MA, Tabbers MA. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. *PLoS One.* 2015;10(5):e0126982.

75. What are FGIDs in children and adolescents?

Functional nausea and vomiting disorders

- Cyclic vomiting syndrome
- Functional nausea and vomiting syndrome
- Rumination syndrome
- Aerophagia

FAP disorders

- Functional dyspepsia
- IBS
- Abdominal migraine

Functional defecation disorders

- Functional constipation
- Nonretentive fecal incontinence

Hyams JS, DiLorenzo C, Saps M, et al. Functional disorders: children and adolescents. *Gastroenterology.* 2016;150(6):1457.

76. What clinical features characterize IBS?

IBS is a well-characterized set of recurrent, replicable features that have abdominal pain at least 4 days per month for at least 2 months associated with at least two of the following three symptoms: **pain related to defecation**, **change in the frequency of stool**, and **change in the form of stool**. Thus, there is commonly a pattern of alternating diarrhea and constipation.

Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med.* 2017;376(26):2566–2578.

77. A 12-year-old who presents with weight loss and a history of effortlessly and involuntarily regurgitating many meals has what likely diagnosis?

Rumination syndrome. This is a functional GI motility disorder characterized by repetitive, effortless regurgitation of recently swallowed food from the stomach into the mouth within 30 minutes of ingesting the meal. When the stomach contents reach the mouth, it is either reswallowed or expelled. In infants and young children, rumination is commonly seen in patients with neurologic impairment or developmental delay. Adolescents are typically healthy. Children who have rumination typically do not retch and do not complain of dyspeptic/heartburn symptoms. Rumination syndrome can be difficult to diagnose; esophageal manometry is used, but not all patients can cooperate for the test. Differential diagnoses include bulimia nervosa and gastroparesis. The most effective treatments involve biofeedback and relaxation techniques.

Kessing BF, Smout AJ, Bredenoord AJ. Current diagnosis and management of the rumination syndrome. *J Clin Gastroenterol.* 2014; 48(6):478–483.

78. Why is abdominal migraine more of a headache for children than for adults?

Abdominal migraine is an FGID that typically affects children between 3 and 10 years, with a peak age at diagnosis of 7 years. Persistence into adulthood does not occur for the majority of patients. Abdominal migraine in childhood is likely underdiagnosed due to lack of recognition by the medical community. Features include at least two episodes of acute, intense, incapacitating paroxysmal abdominal pain (periumbilical, midline, or diffuse), which are stereotypical for the patient and last $\geq$1 hour (mean duration is 17 hours). These episodes are separated by weeks to months with symptom-free intervals. The pain is associated with two or more of the following symptoms/signs: anorexia, nausea, vomiting, headache, photophobia, or vasomotor symptoms (flushing or pallor). Headache is actually an uncommon feature during most episodes, although a patient or family history of migraine headaches is quite common. Compared with cyclic vomiting syndrome, the vomiting in abdominal migraine is less prominent. Abdominal migraine likely shares pathophysiologic features with migraine headache, as there can be commonality of triggers (e.g., stress, fatigue, travel) and of relief by rest and sleep. Prophylactic therapy of various types, including pizotifen (a serotonin and histamine antagonist), amitriptyline, propranolol, and cyproheptadine, has been successful. Nonpharmacologic therapy (e.g., cognitive behavioral therapy) has shown promising results. Because abdominal migraine can share overlapping features with cyclic vomiting syndrome and migraine headaches without aura, distinctions are sometimes difficult.

Irwin S, Barmherzig R, Gelfand A. Recurrent gastrointestinal disturbance: abdominal migraine and cyclic vomiting syndrome. *Curr Neurol Neurosci Rep.* 2017;17(3):21.

Napthali K, Koloski N, Talley NJ. Abdominal migraine. *Cephalalgia.* 2016;36(10):980–986.

Hyams JS, DiLorenzo C, Saps M, et al. Functional disorders: children and adolescents. *Gastroenterology.* 2016;150(6): 1462–1463.

79. How cyclic is cyclic vomiting?

Per Rome IV criteria, two or more episodes of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-month period, are potentially features of cyclic vomiting. These episodes are stereotypical in each patient, and during the interval of weeks to months, the patient returns to baseline health and vomiting cannot be attributed to another condition. Nearly one-half of patients with this diagnosis will have onset <3 years of age.

Any testing for neurometabolic disease is ideally done during the vomiting episode and before intravenous fluids. In adolescents with possible chronic use of cannabis, consider cannabinoid hyperemesis syndrome, which can feature repeated episodes of severe vomiting, nausea, and abdominal pain. Treatment for cyclic vomiting is cyproheptadine for patients <5 years and amitriptyline for patients >5 years.

Hyams JS, DiLorenzo C, Saps M, et al. Functional disorders: children and adolescents. *Gastroenterology.* 2016;150(6):1457.

80. In children with abdominal pain, what historical features suggest a possible organic or serious cause?

- Involuntary weight loss
- Deceleration of linear growth
- GI blood loss (guaiac-positive stools)
- Significant vomiting (e.g., bilious emesis, hematemesis, protracted vomiting, cyclical vomiting)
- Difficulty swallowing/painful swallowing (odynophagia)
- Chronic, severe diarrhea (especially nighttime diarrhea)
- Alarming signs on abdominal examination (right upper or lower quadrant tenderness, localized fullness or mass effect, peritoneal signs, hepatomegaly, splenomegaly, costovertebral angle tenderness, perirectal disease)
- Unexplained fevers
- Arthritis
- Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease

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Hyams JS, DiLorenzo C, Saps M, et al. Functional disorders: children and adolescents. *Gastroenterology.* 2016;150(6):1460.
Di Lorenzo C, Colletti RB, Lehmann HP, et al. Chronic abdominal pain in children: a clinical report of the American Academy of Pediatrics and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2005;40(3):245–248.

81. What treatments are used for FAP in children?

- **Dietary:** Low-lactose diets, dietary fiber, low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diets, probiotics
- **Pharmacologic:** Antidepressants, antispasmodics, prokinetic agents, H2-receptor antagonists
- **Psychological:** Cognitive behavioral therapy, family intervention, relaxation, and distraction techniques
- **Complementary and alternative medicine:** Herbal medicine, peppermint oil, biofeedback, hypnotherapy, massage therapy, acupuncture

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Rutten JM, Korterink JJ, Venmans LM, et al. Nonpharmacologic treatment of functional abdominal pain disorders: a systematic review. *Pediatrics.* 2015;135(3):522–535.
Korterink JJ, Rutten JM, Venmans LM, et al. Pharmacologic treatment in pediatric functional abdominal pain disorders: a systematic review. *J Pediatr.* 2015;166(2):424–431.

GASTROINTESTINAL BLEEDING

82. What features on physical examination can help identify an unknown cause of GI bleeding?

See Table 7.4.

Kamath BK, Mamula P. Gastrointestinal bleeding. In Liacouras CA, Piccoli DA, eds. *Pediatric Gastroenterology: The Requisites in Pediatrics*. Philadelphia, PA: Mosby; 2008;87–97.

Table 7.4 Features to Identify the Cause of Gastrointestinal Bleeding

Skin	Signs of chronic liver disease (e.g., spider angiomas, venous distention, caput medusae, jaundice) Signs of coagulopathy (e.g., petechiae, purpura) Signs of vascular dysplasias (e.g., telangiectasia, hemangiomas) Signs of vasculitis (e.g., palpable purpura on legs and buttocks suggests Henoch-Schönlein purpura) Dermatologic manifestations of IBD (e.g., erythema nodosum, pyoderma gangrenosum)

Table 7.4 Features to Identify the Cause of Gastrointestinal Bleeding (*Continued*)

Head and neck	Signs of epistaxis (especially before placing a nasogastric tube, which can induce bleeding) Hyperpigmented spots on the lips and gums (suggests Peutz-Jeghers syndrome, which is associated with multiple intestinal polyps) Webbed neck (suggests Turner syndrome, which is associated with gastrointestinal vascular malformations and IBD) Lesions on buccal mucosa (suggests trauma)
Lungs	Hemoptysis (tuberculosis, pulmonary hemosiderosis)
Cardiac	Murmur of aortic stenosis (in adults, associated with vascular malformations of the ascending colon, although this association is not certain in children)
Abdomen	Splenomegaly or hepatomegaly (suggests portal hypertension and possible esophageal varices) Ascites (suggests chronic liver disease and possible varices) Palpable or tender loops of intestine (suggests IBD)
Joint	Arthritis (Henoch-Schönlein purpura, IBD)
Perianal	Perianal ulcerations and skin tags (suggest IBD) Perianal abscess (suggests IBD, chronic granulomatous disease immunodeficiency) Fissure (suggests constipation) Hemorrhoids (suggests constipation, portal hypertension) Rectal mass on digital examination (suggests polyp)
Growth	Failure to thrive (IBD, Hirschsprung disease)

IBD, Inflammatory bowel disease.

83. In patients with acute GI bleeding, how may vital signs indicate the extent of volume depletion?

It is important to remember that when acute bleeding occurs in children, it may take 12 to 72 hours for full equilibration of a patient's hemoglobin to occur. Vital signs are much more useful for patient management in the acute setting (Table 7.5).

Mezoff AG, Preud'homme DL. How serious is that GI bleed? *Contemp Pediatr.* 1994;11:60–92.

Table 7.5 Vital Signs and Blood Volume Loss

VITAL SIGNS	BLOOD VOLUME LOSS
Tachycardia without orthostasis	5%-10% loss
Orthostatic changes Pulse increases by 20 beats/min Blood pressure decreases by 10 mm Hg	>10% loss
Hypotension and resting tachycardia	30% loss
Nonpalpable pulses	>40% loss

84. When is endoscopy performed in the setting of a GI bleed?

Endoscopy is an important tool for identifying and containing the source of a GI bleed, but it should only be performed after any required fluid and blood resuscitation. Ideally, patients with blood loss resulting in severe acute anemia should be transfused over several hours and hemoglobin should be rechecked and vital signs stable before endoscopy under general anesthesia. If profuse bleeding persists, endoscopy may be warranted sooner to control the bleeding. Additional medications, including octreotide, may be utilized to vasoconstrict splanchnic circulation to slow down bleeding. This is especially important in bleeding due to varices to stabilize the child before endoscopy with sclerotherapy or banding of varices.

85. How does the type of bloody stool help pinpoint the location of a GI bleed?

- **Hematochezia** (bright red blood): Normal stool spotting on toilet tissue likely suggests distal bleeding (e.g., anal fissure, juvenile colonic polyp). Mucus or diarrheal stools (especially if painful) indicate left-sided or diffuse colitis.
- **Melena** (black, tarry stools) indicates blood denatured by acid and usually implies a proximal lesion, likely before the ligament of Treitz. However, melena can be seen in patients with Meckel diverticulum as a result of denaturation by anomalous gastric mucosa.

- **Currant jelly** (dark maroon) stools usually come from the distal ileum or colon and often are associated with ischemia (e.g., intussusception).

Because blood is a cathartic, intestinal transit time can be greatly accelerated and makes defining the site of bleeding by the magnitude and color of the blood difficult. This difficulty underscores the importance of the initial nasogastric tube insertion.

86. What can cause false-negative and false-positive results when testing stools for blood?

Hemoglobin and its various derivatives (e.g., oxyhemoglobin, reduced hemoglobin, methemoglobin, carboxyhemoglobin) can serve as catalysts for the oxidation of guaiac (Hemoccult) or benzidine (Hematest) when a hydrogen peroxide developer is added, thereby producing a color change. Of note, iron does not cause false-positive results.

- **False negatives:** Ingestion of large doses of ascorbic acid; delayed transit time or bacterial overgrowth, allowing bacteria to degrade the hemoglobin to porphyrin
- **False positives:** Recent ingestion of red meat or peroxidase-containing fruits and vegetables (e.g., broccoli, radishes, cauliflower, cantaloupes, turnips)

87. How do the causes of *lower* GI bleeding vary by age group?

Newborn and infant:

- *Mucosal:* Anal fissure, infectious colitis, eosinophilic or allergic colitis, Hirschsprung enterocolitis, necrotizing enterocolitis
- *Structural:* Intestinal duplication, Meckel diverticulum, intussusception

Child:

- *Mucosal:* Anal fissure, juvenile polyp, infectious colitis, IBD, solitary rectal ulcer, lymphonodular hyperplasia
- *Structural:* Intestinal duplication, Meckel diverticulum, intussusception, volvulus, Dieulafoy malformation (large tortuous arteriole in the stomach that erodes and bleeds)
- *Other:* HUS, Henoch-Schönlein purpura, factitious disorder imposed on another (FDIA, formerly Munchausen syndrome by proxy), arteriovenous malformation, vascular malformation

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Pai AK, Fox VL. Gastrointestinal bleeding and management. *Pediatr Clin North Am.* 2017;64(3):543–561.

Kamath BK, Mamula P. Gastrointestinal bleeding. In Liacouras CA, Piccoli DA, eds. *Pediatric Gastroenterology: The Requisites in Pediatrics*. Philadelphia, PA: Mosby; 2008:87–97.

88. A previously asymptomatic 18-month-old child has large amounts of painless rectal bleeding (red but mixed with darker clots). What is the likely diagnosis?

Although juvenile polyps can also cause painless rectal bleeding, the likely diagnosis is a **Meckel diverticulum**. This outpouching occurs from the failure of the intestinal end of the omphalomesenteric duct to obliterate (Fig. 7.8).

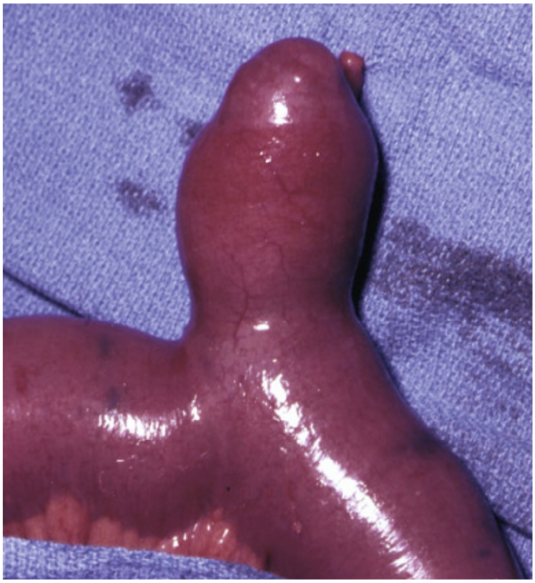

Fig. 7.8 Meckel diverticulum projecting from the antimesenteric border of the ileum. (From Towsend CM Jr, Beauchamp RD, Evers BM, Mattox KL, eds. *Sabiston Textbook of Surgery*. 20th ed. Philadelphia, PA: Elsevier; 2017:1284).

Up to 2% of the population may have a Meckel diverticulum, and about half contain gastric mucosa; most are usually silent throughout life. Meckel diverticulum is twice as common in males and usually appears during the first 2 years of life as massive painless bleeding that is red or maroon in color. Tarry stools are observed in about 10% of cases. A history of previous minor episodes may be obtained. The presentation can range from shock to intussusception with obstruction, volvulus, or torsion. Meckel diverticulitis, which occurs in 10% to 20% of cases, may be indistinguishable from appendicitis.

89. Worldwide, what is the most common cause of GI blood loss in children?

Hookworm infection. Caused by the parasites *Necator americanus* and *Ancylostoma duodenale,* this infection is often asymptomatic. Progressive microscopic blood loss often leads to anemia as a result of iron deficiency.

Loukas A, Hotez PJ, Diemert D, et al. Hookworm infection. *Nat Rev Dis Primers*. 2016;2:16088.
Crompton DW. The public health importance of hookworm disease. *Parasitology.* 2000;121 Suppl:S39–S50.

90. How do the causes of *upper* GI bleeding vary by age group?

- **Newborns:** swallowed maternal blood, vitamin K deficiency, stress gastritis or ulcer, vascular anomaly, coagulopathy, milk-protein sensitivity
- **Infants:** stress gastritis or ulcer, acid-peptic disease, Mallory-Weiss tear, vascular anomaly, GI duplications, gastric or esophageal varices, duodenal or gastric webs, bowel obstruction
- **Children:** Mallory-Weiss tear, acid-peptic disease, varices, caustic ingestion, vasculitis, hemobilia, tumor

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Gilgar MA. Upper gastrointestinal bleeding. In Walker WA, Goulet O, Kleinman RE, et al, eds. *Pediatric Gastrointestinal Disease*. 4th ed. Hamilton, Ontario: B.C. Decker; 2004:258–265.

91. What is the most likely cause of hematemesis in a healthy term infant?

Swallowed maternal blood. The *Apt test* can be used to differentiate maternal from infant blood. Fetal hemoglobin resists denaturation with alkali better than adult hemoglobin does. Therefore exposure of adult blood to sodium hydroxide will result in a brown color, whereas the newborn infant's blood will remain pink.

92. What are the two most likely causes of visible blood in the stool of an otherwise healthy infant?

Anal/rectal fissure and **food protein–induced proctocolitis (milk/soy protein allergy)**. A physical examination and rectal examination are of particular importance in making the diagnosis.

KEY POINTS: GASTROINTESTINAL BLEEDING

1. Hemoglobin measurement is a much less reliable indicator of volume depletion than vital signs during the assessment of acute GI bleeding.
2. Endoscopic evaluation is indicated for some forms of GI bleeding after appropriate fluid and packed red blood cell (pRBC) resuscitation. Endoscopy can be both diagnostic and therapeutic depending on the etiology of the bleed.
3. The two most common causes of painless rectal bleeding in children are juvenile polyps and Meckel diverticulum.

93. What are the six most common causes of massive GI bleeding in children?

1. Esophageal varices
2. Meckel diverticulum
3. Hemorrhagic gastritis
4. Crohn disease (CD) with ileal ulcer
5. Peptic ulcer (mainly duodenal)
6. Arteriovenous malformation

Treem WR. Gastrointestinal bleeding in children. *Gastrointest Endosc Clin North Am.* 1994;4(1):75–97.

94. What is the most common clinical presentation of juvenile polyps in children?

Painless, rectal bleeding. Up to one-third of patients can have chronic blood loss with microcytic anemia. The peak prevalence in children is between 1 and 7 years of age. The polyps are most commonly found in the rectum. Large polyps can be the lead point for intussusception.

95. What are the types of colonic polyps?

- **Malignant:** polyps with cells that have lost their normal differentiation (including adenomas, some of which have the ability to become cancerous)
- **Hamartomatous:** benign focal malformations composed of tissue elements normally found at that site but growing in a disorganized manner
- **Hyperplastic:** a serrated polyp without malignant potential
- **Inflammatory:** polyps associated with IBDs

96. Why is it important to confirm a diagnosis of juvenile polyposis?

Juvenile polyposis syndrome is diagnosed in children with any of the following criteria: (1) five or more polyps in the colon/rectum, (2) juvenile polyps throughout the GI tract, or (3) any number of juvenile polyps and a family history of juvenile polyposis syndrome. The inheritance of this syndrome is autosomal dominant. It is common (up to 12%) in patients with symptomatic polyps, especially with right colonic polyps, anemia, and adenomas rather than hamartomas.

The importance of establishing a diagnosis of a polyposis syndrome is that some syndromes (e.g., Peutz-Jeghers and juvenile polyposis syndrome) are associated with a **risk for developing adenocarcinoma**, with an incidence as high as 30% in as few as 10 years after diagnosis. Another feature of Peutz-Jeghers syndrome is the presence of characteristic small, dark-colored spots (melanosis) on the lips, inside the mouth, and near the eyes and nostrils (Fig. 7.9).

Brosens LAA, Langeveld D, van Hattem WA, et al. Juvenile polyposis syndrome. *World J Gastroenterol.* 2011;17(44):4839–4844.

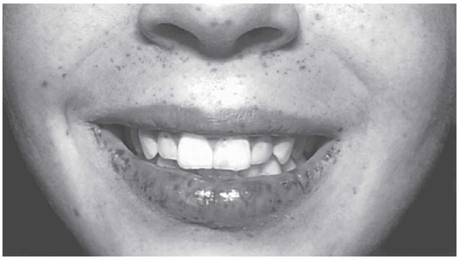

Fig. 7.9 Macular pigmented lesions in patient with Peutz-Jeghers syndrome. (From Kliegman RM, Stanton BF, St. Geme JW, et al, eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Saunders; 2011:1362.e5.)

GASTROINTESTINAL DYSMOTILITY

97. What are the common symptoms of gastroparesis?

Gastroparesis is a disorder of gastric motility characterized by impairment of gastric contraction and emptying. Common symptoms include bloating, early satiety, nausea, vomiting (especially of undigested food eaten many hours before), and abdominal discomfort in the absence of mechanical obstruction.

98. In what clinical settings should gastroparesis be suspected?

- Preterm infants with an immature GI tract
- Infants with cow milk protein allergy
- Postinfectious, including viral (rotavirus, Epstein-Barr virus [EBV], cytomegalovirus [CMV]) and *Mycoplasma* infection
- Postsurgical, including vagal nerve injury in upper abdominal surgery such as fundoplication or bariatric surgery
- Cystic fibrosis
- Type 1 diabetes mellitus
- Chronic intestinal pseudo-obstruction
- Muscular dystrophy
- Systemic autoimmune disorders, such as scleroderma or CD
- Medication side effects: anticholinergics, opioids, tricyclic antidepressants, diphenhydramine, proton pump inhibitors, H2-receptor antagonists, and others

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Islam S. Gastroparesis in children. *Curr Opin Pediatr.* 2015;27(3):377–382.

99. How is postinfectious gastroparesis diagnosed?

Patients will commonly present with persistent vomiting for days, weeks, or even months after a viral illness. Often the acute illness has passed, and the offending pathogen cannot be isolated. Diagnosis is mainly clinical but can be confirmed with a delayed gastric emptying scan.

Saliakellis E, Fotoulaki M. Gastroparesis in children. *Ann Gastroenterol.* 2013;26(3):204–211.

100. How is gastroparesis treated?

- **Dietary and behavioral modifications:** small-volume, more frequent meals are often better tolerated. Limiting fat and fiber content may help promote stomach emptying. Avoidance of carbonated beverages, which can distend the stomach; drinking fluids throughout a meal; and walking 1 to 2 hours after a meal can promote better stomach emptying. In severe cases, a majority of calories can be provided in liquid form.

- **Pharmacotherapy:** *Prokinetic agents,* including (1) dopamine receptor antagonists (e.g., metoclopramide), which increase duration and frequency of antral and duodenal contractions, increase LES pressure, and relax the pyloric sphincter; and (2) erythromycin, a macrolide antibiotic with agonist activity of motilin receptors in smooth muscle cells of the GI tract (stomach and small bowel). Long-term use of metoclopramide at high doses puts children at risk for persistent tardive dyskinesia and has led to a "black box" warning by the U.S. Food and Drug Administration (FDA). Botulinum toxin injected endoscopically to the pylorus muscle can be used in refractory cases of gastroparesis.

Saps M, DiLorenzo C. Gastric motility disorders. In Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal and Liver Disease.* Philadelphia, PA: Elsevier Saunders; 2011:316–317.

101. What is chronic intestinal pseudo-obstruction?

Chronic intestinal pseudo-obstruction (CIP) is a rare, disabling disorder characterized by signs and symptoms of GI obstruction in the absence of a fixed obstructing lesion. Symptoms include abdominal pain, abdominal distention, nausea, vomiting, and constipation or diarrhea. Chronic problems can result in FTT and weight loss. Radiologic studies will demonstrate dilated bowel and the presence of air–fluid levels. CIP can be idiopathic, congenital, or may occur as a secondary manifestation of an underlying condition, such as a chromosomal malformation or an infectious process. The most common infectious cause of CIP worldwide is Chagas disease. Full-thickness biopsies of the intestinal wall reveal histologic abnormalities of the muscle and/or nerve. Treatment includes nutritional support, pharmacotherapy, and sometimes surgery.

Di Nardo G, Di Lorenzo C, Lauro A, et al. Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options. *Neurogastroenterol Motil.* 2017;29(1):12945.

Hyman P. Chronic intestinal pseudo-obstruction. In Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal and Liver Disease.* 4th ed. Philadelphia, PA: Elsevier Saunders; 2011:505–511.

GASTROESOPHAGEAL REFLUX

102. Is GER normal?

GER is the involuntary passage of gastric contents into the esophagus, which occurs several times per day in every human, especially after eating, and is physiologically normal. Typically, reflux episodes are transient, asymptomatic, and do not go above the distal esophagus. The pathophysiologic underpinnings of reflux include genetic, environmental (e.g., diet and smoking), anatomic, hormonal, and neurogenic factors. *GERD* occurs when reflux results in symptoms or complications.

Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66(3):516–554.

103. How rapidly do infants outgrow GER?

Forty percent of healthy infants have spitting or regurgitation more than once a day; mild reflux does not represent disease. In infants who have more significant primary GER (about 12% of total), 25% to 50% resolve by 6 months of age, 75% to 85% by 12 months of age, and 95% to 98% by 18 months of age. GER in older children may be more widespread than appreciated. Surveys of parents of children and adolescents (3 to 17 years) revealed that symptoms of heartburn regurgitation were relatively common (2% to 8% of patients).

Campanozzi A, Boccia G, Pensabene L, et al. Prevalence and natural history of gastroesophageal reflux: pediatric prospective study. *J Pediatr.* 2009;123(3):779–783.

104. When does GER become GERD?

GERD occurs when physiologic GER (a variation of normal; "happy spitters" in infants) becomes pathologic with the onset of symptoms and complications. These could include feeding refusal, poor weight gain, painful emesis, chronic respiratory problems, irritability, dystonic neck posturing, heartburn, hematemesis, dysphagia, and others. The delineation can be imprecise, and other medical conditions can present with symptoms similar to GERD or with secondary GERD.

Mousa H, Hassan M. Gastroesophageal reflux disease. *Pediatr Clin North Am.* 2017;64(3):487–505.

Grossman AB, Liacouras CA. Gastrointestinal bleeding. In Liacouras CA, Piccoli DA, eds. *Pediatric Gastroenterology: The Requisites in Pediatrics.* Philadelphia, PA: Mosby; 2008:74–86.

105. What are the diagnostic methods for GER?

The diagnosis can be made either clinically or by diagnostic testing. Clinically, reflux should be suspected in any child who demonstrates frequent, effortless vomiting or regurgitation without evidence of GI obstruction. Clinical response to medical therapy can be diagnostic.

The **upper GI barium** study does not reliably indicate reflux but can assess for anatomic abnormalities, such as malrotation, which might contribute. **Nuclear scintigraphy**, a noninvasive test that uses radiolabeled milk ("milk scan") or a meal ("gastric emptying test"), can detect postprandial reflux and delay in gastric emptying but cannot distinguish between physiologic and pathologic reflux. The presence of histologic esophagitis on an endoscopic examination is suggestive, but not diagnostic, of reflux; the absence of esophagitis does not rule out reflux. The **24-hour pH probe**, traditionally thought to be the most reliable test for the diagnosis of GER, only detects acid reflux and cannot detect nonacid reflux. **Multichannel intraluminal impedance** can be performed along with a pH probe to assess all types of reflux—acid, weakly acid, and alkaline—and can assess how proximal within the esophagus the reflux reaches. It is often used in combination with pH probe testing to separate acid from nonacid reflux.

Shin MS. Esophageal pH and combined impedance-pH monitoring in children. *Pediatr Gastroenterol Hepatol Nutr.* 2014;17(1):13–22.
van der Pol RJ, Smits MJ, Venmans L, et al. Diagnostic accuracy of tests in pediatric gastroesophageal reflux disease. *J Pediatr.* 2013; 162(5):983–987.

106. How effective are nonpharmacologic agents as treatments for suspected GER?

They can be quite effective clinically. In a study of infants with suspected GER, the following changes resulted in improvements after 2 weeks in reflux scores in three-quarters and normalization in one-quarter of patients:

- Switching formula-fed infants to semi-elemental formula thickened with rice cereal
- If breastfeeding, elimination of cow milk and soy products from mother's diet
- Avoiding seated and supine positioning as much as possible for the infant, especially after feeding
- Eliminating tobacco smoke because of its association with increased GERD

Orenstein SR, McGowan JD. Efficacy of conservative therapy as taught in the primary care setting for symptoms suggesting infant gastroesophageal reflux. *J Pediatr.* 2008;152(3):310–314.

107. How effective are H2 blockers and proton pump inhibitors in the treatment of GER?

These medications, though widely prescribed, especially in infants, have not been shown to be efficacious by a preponderance of studies. Part of the lack of demonstrated clinical success may be that many symptoms blamed on GER (such as cough, gagging, desaturations, back arching, fussiness, and pain) and treated with H2 antagonists or proton pump inhibitors are not associated with reflux events when studied with pH-multichannel intraluminal probes. Additionally, there is concern that chronic proton pump inhibitor use in children may be associated with increased risks of respiratory and GI tract infections, vitamin B_{12} deficiency, and bone fractures. Many experts advise caution with these medications, particularly proton pump inhibitors, with routine use reserved for proven esophagitis and not for treatment of symptoms alone.

Bardou M, Fortinsky KJ, Chapelle N, et al. An update on the latest chemical therapies for reflux esophagitis in children. *Expert Opin Pharmacother.* 2019;20(2):231–239.
DeBruyne P, Ito S. Toxicity of long-term use of proton pump inhibitors in children. *Arch Dis Child.* 2018;103(1):78–82.
van der Pol RJ, Smits MJ, van Wijk MP, et al. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. *Pediatrics.* 2011;127(5):925–935.

108. An infant with known GER who periodically arches his or her back may have what syndrome?

Sandifer syndrome is paroxysmal dystonic posturing with opisthotonus and unusual twisting of the head and neck (resembling torticollis) in association with GER. Typically, an esophageal hiatal hernia is also present.

109. What is a Nissen fundoplication?

Nissen fundoplication is the most commonly performed antireflux surgical procedure. It involves wrapping a portion of the gastric fundus 360 degrees around the distal esophagus in an effort to tighten the gastroesophageal junction.

110. Which patients are candidates for fundoplication?

Most infants with developmental GER do not require fundoplication. It is indicated in patients with **recurrent aspiration**, **refractory** or **Barrett esophagitis**, **reflux-associated apnea**, and **reflux-associated FTT** that is refractory to medical therapy. Patients with severe reflux and psychomotor retardation should be evaluated for fundoplication if a feeding gastrostomy is contemplated.

111. What is erosive esophagitis?

Erosive esophagitis is defined as visible breaks in the mucosa of the esophagus. It can be diagnosed by upper endoscopy. In patients with GERD and problematic symptoms, the likelihood of having erosive esophagitis can vary widely. Histopathologic evaluation is recommended to rule out complications such as Barrett esophagitis (a potential premalignant condition with changes in normal epithelium), as well as other underlying causes besides GERD, including EoE. Erosive esophagitis is more frequent in children with GERD and hiatal hernia.

112. When does GERD become NERD?

Reflux with typical symptoms of chest pain, heartburn, and regurgitation but without evidence of visible esophageal mucosal lesions is known as *nonerosive reflux disease (NERD).* This is the most common presentation of GERD in adults. Due to the heterogeneity in this patient population, the use of 24-hour pH and multichannel intraluminal impedance testing is necessary to quantify both acidic and nonacidic reflux and correlate with patient-reported symptoms. This test can help to differentiate among (1) *NERD* with abnormal esophageal acid exposure, (2) *reflux hypersensitivity* with normal esophageal acid exposure but a positive symptom association to acid or nonacid reflux, and (3) *functional heartburn* with normal esophageal acid exposure and a negative symptom association. Unfortunately, clinical symptoms, response to proton pump inhibitors, or endoscopic biopsy findings cannot reliably distinguish these reflux subtypes.

Mahoney LB, Nurko S, Rosen R. The prevalence of Rome IV nonerosive esophageal phenotypes in children. *J Pediatr.* 2017;189:86–91.

KEY POINTS: GASTROESOPHAGEAL REFLUX

1. More than 40% of healthy infants regurgitate effortlessly more than once per day. This does not represent significant GER.
2. GERD is usually a clinical diagnosis. Testing, such as upper GI testing, nuclear scintigraphy, pH and impedance monitoring, and upper endoscopy, can be helpful in certain cases, but it usually is not necessary.
3. By the age of 12 months, the symptoms of 95% of infants with significant reflux have resolved.

HEPATOBILIARY DISEASE

113. How is ascites diagnosed by physical examination?

Severe ascites is commonly diagnosed by observation of the child in a supine and then an upright position. Bulging flanks, umbilical protrusion, and scrotal edema (in males) are generally evident. Three main techniques are used when the diagnosis is not obvious:

- **Fluid wave:** This sign can be elicited in a cooperative patient by tapping sharply on one flank while receiving the wave with the other hand. The transmission of the wave through fatty tissue should be blocked by a hand placed on the center of the abdomen.
- **Shifting dullness:** With the patient supine, percussion of the abdomen will demonstrate a central area of tympany at the top that is surrounded by flank percussion dullness. This dullness shifts when the patient moves laterally or stands up.
- **"Puddle sign":** A cooperative and mobile patient may be examined in the knee–chest position. The pool of ascites is tapped while you listen for a sloshing sound or change in sound transmission with the stethoscope.

Small amounts of ascites can be extremely difficult to detect with physical examination in children. Although ascites can be demonstrated on radiographs, the most sensitive and specific test is an abdominal-pelvic ultrasound, which can detect as little as 150 mL of ascitic fluid.

114. What laboratory tests are commonly used to evaluate liver disease?

See Table 7.6.

Table 7.6 Laboratory Tests Commonly Used to Evaluate Liver Disease

TEST	CLINICAL SIGNIFICANCE
Alanine aminotransferase (ALT, SGPT)	Increased with damaged hepatocytes
Aspartate aminotransferase (AST, SGOT)	Less sensitive than ALT for hepatic injury
Alkaline phosphatase (AP)	Increased in cholestatic disease; also comes from bone Higher in children because of bone growth (can identify source through isoenzyme)
γ-Glutamyltransferase (GGT)	More sensitive marker for cholestasis than AP
Bilirubin	Differential diagnosis different for conjugated versus unconjugated
Albumin	Low albumin can indicate chronic impairment in hepatic synthetic function

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Table 7.6 Laboratory Tests Commonly Used to Evaluate Liver Disease (*Continued*)

TEST	CLINICAL SIGNIFICANCE
Prealbumin	Shorter half-life; may reflect more acute synthetic capabilities
Prothrombin time (PT)	Reflects synthetic function as a result of short half-life of factors
Ammonia	Impaired removal in patients with chronic liver disease; can lead to encephalopathy

115. What conditions are associated with elevations of aminotransferases?

- Steatosis (fatty liver due to metabolic syndrome)
- Hepatocellular inflammation (hepatitis)
- Drug- or toxin-associated hepatic injury
- Hypoperfusion or hypoxia
- Passive congestion (right-sided congestive heart failure, Budd-Chiari syndrome, constrictive pericarditis)
- Nonhepatic disorders (muscular dystrophy, celiac disease, macroenzyme of aspartate aminotransferase)

Teitelbaum JE. Normal hepatobiliary function. In Rudolph CD, Rudolph AM, eds. *Rudolph's Pediatrics*. 21st ed. New York: McGraw-Hill; 2003:1479.

116. What is the most frequent cause of chronically elevated aminotransferases among children and adolescents in the United States?

Nonalcoholic fatty liver disease (NAFLD). The condition is most commonly associated with the metabolic syndrome in obese patients. Hepatic steatosis (abnormal lipid deposition in hepatocytes) occurs in the absence of excess alcohol intake. A main concern of the condition is that this simple benign fatty liver disease may progress to nonalcoholic steatohepatitis (NASH) which involves inflammation of the liver and hepatocellular damage. This ultimately can lead to cirrhosis with possible liver failure and/or hepatocellular carcinoma. It is unclear how and why certain children make that significant pathologic jump to marked liver disease.

Berardis S, Sokal E. Pediatric non-alcoholic fatty liver disease: an increasing public health issue. *Eur J Pediatr.* 2014;173(2):131–139.

117. What is the main reason for the apparent increase in pediatric NAFLD?

The **growing obesity epidemic** is likely responsible. Some studies indicate that about half of obese children may have fatty liver disease. Children of Asian descent and of Hispanic (mostly Mexican) descent are also at increased risk compared with white and black American children.

Nieregarten MB, Freed GL. Pediatric nonalcoholic fatty liver disease. *Contemp Pediatr.* 2013;30:14.

118. What is the best way to screen for NAFLD?

Established screening guidelines are currently lacking. The most widely used test is **serum alanine aminotransferase (ALT)**, which is the most common abnormal laboratory finding noted in the disease, but the sensitivity is low. In addition, the height of the measurement does not correlate with disease severity. Conversely, normal levels do not exclude possible fibrosis. Imaging studies, particularly ultrasound, have some diagnostic merit with potential detection of increased fatty echogenicity and hepatic enlargement. However, ultrasound is diagnostically most effective when hepatic steatosis is more advanced with a liver fat content of $>$30%. Computed tomography (CT) is a better study, but it has obvious radiation implications. The gold standard for diagnosis—liver biopsy—is too invasive as a screening test.

Berardis S, Sokal E. Pediatric non-alcoholic fatty liver disease: an increasing public health issue. *Eur J Pediatr.* 2014;173(2):131–139.

119. What are the treatments for NAFLD?

Diet and exercise to promote weight loss. Other medical therapies should be considered in biopsy-proven NAFLD in patients who have failed lifestyle modifications of diet and exercise, although there are limited long-term data on safety and efficacy. Though the precise mechanism of progression from steatosis to NASH is poorly understood, it is believed that oxidative stress plays an important role in hepatocellular damage. Antioxidant therapy, including vitamin E (RRR-α-tocopherol), has been shown in some studies to improve liver biochemical parameters and histologic changes.

Mencin AA, Loomba R, Lavine JE. Caring for children with NAFLD and navigating their care into adulthood. *Nat Rev Gastroenterol Hepatol.* 2015;12(11):617–628.

Sato K, Gosho, M, Yanamoto T, et al. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Nutrition.* 2015;31(7–8):923–930.

120. Why is it important to determine whether an elevated bilirubin is conjugated or unconjugated?

Bilirubin released from erythrocytes (unconjugated) is taken up by the liver and enzymatically converted (conjugated) to a more water-soluble form. On the basis of laboratory methodology, measurements of unconjugated bilirubin are referred to as *indirect reacting* and those of conjugated bilirubin as *direct reacting*. Unbound unconjugated bilirubin can cross the blood–brain barrier and is toxic to the CNS. Elevated conjugated bilirubin is associated with obstruction of the biliary tract, intrahepatic cholestasis, or poorly functioning hepatocytes. Conjugated hyperbilirubinemia always requires further evaluation.

Harb R, Thomas DW. Conjugated hyperbilirubinemia: screening and treatment in older infants and children. *Pediatr Rev.* 2007; 28(3):83–90.

121. When are levels of conjugated bilirubin considered abnormal?

Conjugated or direct hyperbilirubinemia is defined as a direct bilirubin concentration >1 mg/dL when the total serum bilirubin concentration is ≤ 5 mg/dL. If the total serum bilirubin concentration is >5 mg/dL, direct hyperbilirubinemia is present when the value is 20% or greater of the total bilirubin concentration.

Lauer BJ, Spector ND. Hyperbilirubinemia in the newborn. *Pediatr Rev.* 2011;32(8):341–349.

122. What are the common causes of neonatal hepatitis and neonatal cholestasis?

See Table 7.7.

123. What is the likelihood of chronic hepatic disease developing after acute infections with hepatitis viruses A to G?

Table 7.7 Neonatal Conjugated Hyperbilirubinemia and Neonatal Hepatitis

Neonatal Hepatitis
Idiopathic
Viral
Cytomegalovirus
Herpesviruses
Hepatitis viruses
Human immunodeficiency virus
Enterovirus
Rubella
Adenovirus
Bacterial
Bile Duct Obstruction
Biliary atresia
Choledochal cyst
Neonatal sclerosing cholangitis
Congenital hepatic fibrosis
Cholelithiasis
Tumor or mass

Metabolic
α_1-Antitrypsin deficiency
Tyrosinemia
Galactosemia
Cystic fibrosis
Bile acid synthetic disorders
Storage disorders
Niemann-Pick disease
Gaucher disease
Lipidoses
Peroxisomal disorders
Endocrine
Hypothyroidism
Panhypopituitarism
Other Inherited Causes
Alagille syndrome
Familial intrahepatic cholestasis
Neonatal iron storage disease
Toxic
Parenteral nutrition
Drugs
Cardiovascular Disorders

Adapted from Suchy FJ. Approach to the infant with cholestasis. In Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children.* 3rd ed. New York: Cambridge University Press; 2007:179–189.

- *Hepatitis A:* 95% recover within 1 to 2 weeks of illness; chronic disease is unusual
- *Hepatitis B:* >90% of perinatally infected infants develop chronic hepatitis B infection; 25% to 50% of children who acquire the virus between 1 and 5 years of age develop chronic infection; in older children and adults, only 6% to 10% develop chronic infection
- *Hepatitis C:* 50% to 60% develop persistent infection

- *Hepatitis D:* Occurs only in patients with acute or chronic hepatitis B infection; 80% develop viral persistence
- *Hepatitis E:* Does not cause chronic hepatitis

American Academy of Pediatrics. Hepatitis A-G. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *2018 Red Book, Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:392–437.

124. Other than viral hepatitis, what are other common causes of acute and chronic hepatitis in children?

- **Metabolic and genetic disorders:** Wilson disease, α_1-antitrypsin deficiency, cystic fibrosis, steatohepatitis
- **Toxic hepatitis:** drugs, hepatotoxins, radiation
- **Autoimmune:** autoimmune hepatitis, primary sclerosing cholangitis: anti–smooth muscle antibody positive, anti–liver-kidney-microsomal antibody positive
- **Anatomic**: cholelithiasis, choledochal cyst
- **Other infectious:** CMV, EBV
- **Toxic:** ethanol, acetaminophen
- **Other inherited:** Alagille syndrome, cystic fibrosis, familial intrahepatic cholestasis

125. How is α_1-antitrypsin deficiency most likely to present in infants and children?

α_1-Antitrypsin deficiency is an autosomal recessive disorder that causes lung and liver disease. In the liver, injury results from intracellular accumulation of the mutant α_1-antitrypsin protein. In the lungs, the absence of functional α_1-antitrypsin leads to unchecked leukocyte elastase function, resulting in destruction of the alveolar walls and eventual emphysema. The pulmonary effects take years to evolve, so lung disease rarely is present in children. More common presenting symptoms are neonatal cholestasis, hepatomegaly, and chronic hepatitis. Although most patients do not have severe disease, this can progress to cirrhosis with liver failure.

Stockley RA. Alpha 1-antitrypsin review. *Clin Chest Med.* 2014;35(1):39–50.

126. Why is measuring the serum level of α_1-antitrypsin not enough to diagnose α_1-antitrypsin deficiency?

α_1-Antitrypsin is an acute-phase reactant and might not be decreased in all cases of α_1-antitrypsin deficiency. Pi typing (short for protease inhibitor typing) by electrophoresis is necessary to make the diagnosis. MM is the normal phenotype and has the highest activity; ZZ has the lowest activity and the most common association with liver disease. PiMM is the most common Pi type, with a distribution of about 87%; PiMS represents 8% and PiMZ 2%. The incidence of PiZZ ranges between 1 in 2000 and 1 in 5000.

Silverman EK, Sandhaus RA. Alpha$_1$-antitrypsin deficiency. *N Engl J Med.* 2009;360(26):2749–2757.

127. What is the metabolic defect in patients with Wilson disease?

Wilson disease is an autosomal recessive **defect of copper metabolism** that results in markedly increased levels of copper in many tissues, most notably the liver, basal ganglia, and cornea. Deposition in the cornea results in Kayser-Fleischer rings (Fig. 7.10). The primary defect in Wilson disease is a mutation in the transmembrane protein ATP7B, which is key to excreting excess copper into the biliary canalicular system. The combination of

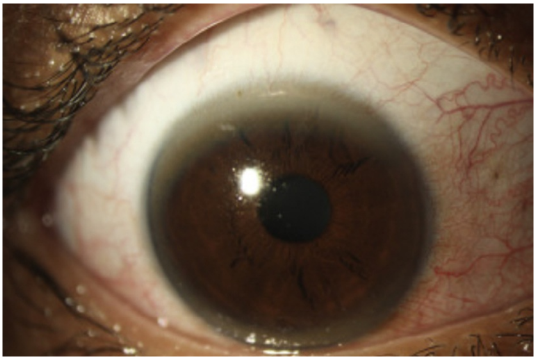

Fig. 7.10 Kayser-Fleischer ring, a brownish discoloration of the outer margin of the cornea due to the accumulation of copper, as seen in this 8-year-old with Wilson disease. (From Koay CL, Zahari M, Lee WS. Kayser-Fleischer ring and sunflower cataract in a child with Wilson's disease. *Pediatr Neonatol.* 2017;58(1):97.)

markedly increased copper levels in a liver biopsy specimen, low serum ceruloplasmin, and increased urinary copper excretion strongly suggests Wilson disease.

Schilsky ML. Wilson disease: diagnosis, treatment and followup. *Clin Liver Dis*. 2017;21(4):755–767.
Ala A, Walker AP, Ashkan K, et al. Wilson's disease. *Lancet.* 2007;369(9559):397–408.

128. What are the treatments of choice for Wilson disease?

Copper-chelating agents. *D-Penicillamine* has traditionally been the drug of choice, but another chelator, *trientine*, has been used successfully in patients who have discontinued penicillamine because of hypersensitivity reactions. Some advocate for trientine as an alternative agent to penicillamine because trientine has a better safety profile. Zinc sulfate, which inhibits intestinal copper absorption, has also been used. Patients require a low-copper diet for life.

129. A 10-year-old child who experiences mild fluctuating jaundice in times of illness, "just like his Uncle Kevin," is likely to have what condition?

Gilbert syndrome, which is due primarily to a decrease in hepatic glucuronyl transferase activity. Normally, bilirubin is disconjugated to glucuronic acid. In patients with Gilbert syndrome, the defective total conjugation results in the increased production of monoglucuronides in bile and mild elevation in serum unconjugated (indirect) bilirubin. The syndrome is inherited in an autosomal dominant fashion with incomplete penetrance (boys outnumber girls by 4 to 1). The frequency of this gene in the population is estimated at 2% to 6%. Elevations of bilirubin are noted during times of medical and physical stress, particularly fasting.

Fretzayas A, Moustaki M, Liapi O, Karpathios T. Gilbert syndrome. *Eur J Pediatr*. 2012;171(1):11–15.

130. What are the clinical findings of portal hypertension?

Obstruction of portal flow is manifested by two physical signs: **splenomegaly** and **increased collateral venous circulation**. Collaterals are evident on physical examination in the anus and abdominal wall and are visible by endoscopy in the esophagus. Hemorrhoids may suggest collaterals, but in older patients these are present in high frequency without liver disease, and thus their presence has no predictive value. Dilation of the paraumbilical veins produces a rosette around the umbilicus (the caput medusae), and the dilated superficial veins of the abdominal wall are visible. A venous hum may be present in the subxiphoid region from varices in the falciform ligament.

131. How does autoimmune hepatitis (AIH) typically present?

There are three typical patterns of presentation: (1) *acute hepatitis,* with nonspecific symptoms of malaise, nausea and vomiting, anorexia, jaundice, dark urine, and pale stools; (2) *insidious,* with progressive fatigue, relapsing jaundice, headache, and weight loss; and (3) despite no history of jaundice, patients present with complications of *portal hypertension* (splenomegaly, GI bleeding from varices, and weight loss). Type I AIH is more common and characterized by antineutrophil antibodies and anti–smooth muscle antibodies. Type 2 AIH is characterized by anti–liver-kidney-microsomal antibodies.

132. A patient with liver failure develops confusion. Why worry?

Hepatic encephalopathy can appear as either a rapid progression to coma or as mild fluctuations in mental status over an extended period. A single underlying cause has not been established, but suspected toxins include ammonia, other neurotoxins, and relatively increased γ-aminobutyric acid activity. Management requires the limitation of protein intake, the use of lactulose to promote clearance of ammonia in the stool, antibiotics to reduce ammonia production, intracranial pressure monitoring in advanced cases, and possible peritoneal dialysis for patients in severe coma and before liver transplantation.

133. What is the most common indication for pediatric liver transplantation?

The most common indication is **extrahepatic biliary atresia** with chronic liver failure after a Kasai hepatoportoenterostomy. Other common indications include inborn errors of metabolism (e.g., α_1-antitrypsin deficiency, hereditary tyrosinemia, Wilson disease) and idiopathic fulminant hepatic failure.

134. Calculous and acalculous cholecystitis: what are the differences?

- *Calculous cholecystitis*: Gallstone impaction in the cystic duct results in gallbladder distention edema, biliary stasis, and bacterial overgrowth (e.g., *Escherichia coli, Klebsiella,* enterococci). If untreated, this can lead to gallbladder infarction, gangrene, and perforation.
- *Acalculous cholecystitis:* Gallbladder dysfunction results from a variety of conditions, including major trauma, sepsis/hypotension, and diabetes. Bile stasis results, which can lead to an inflammatory response, ischemia, distention, and, eventually, necrosis of gallbladder tissue.

135. Which patients are at risk for cholelithiasis?

See Table 7.8.

Table 7.8 Patients at Risk for Cholelithiasis

	PIGMENT STONE	CHOLESTEROL STONE
Race	—	Native American
Sex	—	Female
Age	—	Adolescence
Diet	—	Obesity
Total parenteral nutrition	+++	—
Hemolytic disease (especially sickle cell disease, thalassemia, hereditary spherocytosis)	+++	—
Cystic fibrosis	—	+++
Ileal disease	—	+++
Defects in bile salt synthesis	—	+++
Hypertriglyceridemia	—	+++
Diabetes mellitus	—	+++

+++ = increased risk

KEY POINTS: HEPATIC AND BILIARY DISEASE

1. Portal hypertension manifests clinically as splenomegaly and increased collateral venous circulation.
2. Conjugated hyperbilirubinemia in any child is abnormal and deserves further investigation.
3. Extrahepatic biliary atresia is the most common pediatric indication for liver transplantation.
4. The younger the patient, the more likely it is that acute hepatitis B infection will become chronic.

INFLAMMATORY BOWEL DISEASE

136. Is IBD an immune disease?

IBD, which comprises two major disorders (ulcerative colitis [UC] and CD), is the result of a dysregulated immune response to commensal organisms in a genetically susceptible host that results in chronic relapsing inflammation. Depending on the age of onset, the role of genetics and the immune system may differ. Children diagnosed with IBD <6 years old, known as *very-early-onset inflammatory bowel disease* (VEO-IBD), may exhibit a more severe, refractory disease course and have a monogenic defect in immune-mediated genes resulting in unique IBD phenotypes.

Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol.* 2014;20(1):91–99.

137. Is there a genetic susceptibility to IBD?

Genetically determined factors are felt to contribute to an individual's susceptibility to develop IBD. A first-degree relative of a patient with IBD has a 3 to 20 times increased likelihood of developing IBD compared with the general population. More than 200 IBD risk-associated loci have been identified in genome-wide association studies. These individual loci do not confer disease but do increase one's risk. Genetic testing in the general IBD population is not diagnostic, nor is it predictive of the development of IBD in the general population. In children <6 years old with VEO-IBD, gene panels or whole-exome sequencing can help to identify rare genetic variants, which may be causative for the disease. A major challenge in IBD genetics is to harness the increasing array of genetic associations into clinical utility.

McGovern DP, Kugathasan S, Cho JH. Genetics of inflammatory bowel disease. *Gastroenterology.* 2015;149(5):1163–1172.
Imielinski M, Baldassano RN, Griffiths A, et al. Common variants at five new loci associated with early-onset inflammatory bowel disease. *Nat Genet.* 2009;41(12):1335–1340.

138. What is the epidemiology of pediatric IBD?

The incidence and prevalence of IBD in general, and Crohn disease specifically, have increased over recent decades. The most significant increases have occurred in younger children, with increases of 7% in those <6 years old. About 20% of all IBD cases are diagnosed before age 10 years. The mean age of diagnosis of pediatric IBD is 12.5 years. About 10,000 new cases are diagnosed annually. Up to 25% of children who are diagnosed with IBD have a positive family history.

Benchimol E, Bernstein CN, Bitton A, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. *Am J Gastroenterol.* 2017;112:1120–1134.
Glick SR, Carvalho RS. Inflammatory bowel disease. *Pediatr Rev.* 2011;32(1):14–24.

139. How do UC and CD vary in intestinal distribution?

UC is limited to the superficial mucosa of the colon. It typically involves the rectum and extends proximally to a variable extent. UC more commonly involves the entire colon in children than in adults, who more commonly will have limited left-sided disease. **CD**, or regional enteritis, is characterized by transmural inflammation of the bowel that may affect the entire tract from the mouth to the anus. Because of the transmural nature of the inflammation, patients can develop fistulae and abscesses more commonly with CD. The typical cobblestone appearance of CD is produced by crisscrossing ulcerations (Fig. 7.11). Crohn colitis, with no involvement of the small bowel, is more common in younger children and can be difficult to distinguish from UC.

Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med.* 2009;361(21):2066–2078.
Bousvaros A, Antonioli DA, Colletti RB, et al. Differentiating ulcerative colitis from Crohn disease in children and young adults. *J Pediatr Gastroenterol Nutr.* 2007;44(5):653–674.

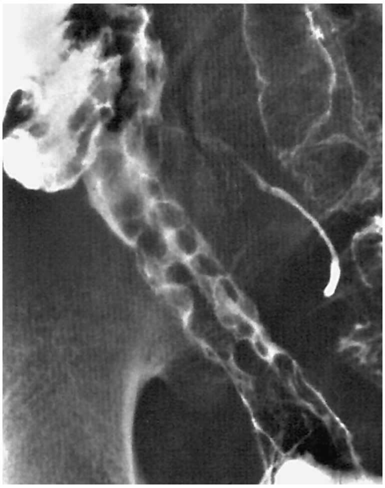

Fig. 7.11 Crisscrossing ulcerations produce a cobblestone appearance in patients with Crohn disease. (From Katz DS, Math KR, Groskin SA. *Radiology Secrets*. Philadelphia, PA: Hanley & Belfus; 1998:150.)

140. What features differentiate UC from CD?

See Table 7.9.

Crohn's and Colitis Foundation of America. www.ccfa.org. Accessed July 3, 2019.

Table 7.9 Features That Differentiate Ulcerative Colitis From Crohn Disease

	ULCERATIVE COLITIS	CROHN DISEASE
Distribution	Colon only (gastritis recognized) Continuous	Entire gastrointestinal tract Skip lesions
Clinical presentation		
Bleeding	Very common	Common
Growth failure	Uncommon	Common
Weight loss	Less common	Common
Obstruction	Uncommon	Common
Perianal disease	Rare	Common

Continued on following page

Table 7.9 Features That Differentiate Ulcerative Colitis From Crohn Disease (*Continued*)

	ULCERATIVE COLITIS	CROHN DISEASE
Endoscopic findings	Continuous inflammation 100% rectal involvement Erythema, edema, friability, ulceration on abnormal mucosa	Focal or segmental inflammation Rectal sparing Aphthous or linear ulcerations on normal-appearing mucosa Cobblestoning Abnormal terminal ileum: $>$50%
Histologic findings	Mucosa only No granulomas	Full-thickness granulomas

141. What are the extraintestinal manifestations of pediatric IBD?

In addition to the typical GI involvement, other organ systems can become involved in IBD. These manifestations may become the major source of morbidity and presenting symptom(s) for some patients.

- **Growth failure**
- **Arthralgias/arthritis**
- **Bone disease**, including osteopenia and osteoporosis
- **Oral lesions**, most commonly recurrent aphthous lesions
- **Skin lesions**: granulomatous, reactive, and secondary to nutritional deficiencies
- **Eye lesions**: episcleritis and uveitis
- **Liver disease**: hepatitis, fatty liver, cholelithiasis, amyloidosis, and primary sclerosing cholangitis
- **Rare extraintestinal manifestations** ($<$1% of pediatric IBD patients): hematologic abnormalities, venous thrombosis, pancreatitis, nephrolithiasis, pulmonary disease, neurologic disease

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Vavricka SR, Schoepfer A, Schari M, et al. Extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2015; 21(8):1982–1992.

Rabizadeh S, Oliva-Hemker M. Extraintestinal manifestations of pediatric inflammatory bowel disease. In Mamula P, Markowitz J, Baldassano R, eds. *Pediatric Inflammatory Bowel Disease*. Philadelphia, PA: Springer; 2007:87–92.

142. What are the goals of therapy for IBD?

The goals of therapy for pediatric IBD are to (1) induce mucosal healing, (2) optimize growth and pubertal development, (3) interrupt the natural history of the disease processes, (4) decrease potential for long-term complications including need for surgical intervention, and (5) maintain quality of life. Overall, the age, presenting symptoms and severity, and sex of the child must be considered when starting therapy. The *top-down therapeutic approach* for moderate to severe disease, starting with biologic therapy with or without a immunomodulator, has been shown to be more effective at achieving the goals of these therapies compared with reaction therapy to acute flares.

Picoraro JA, Rosh JR. Communicating the benefits and risks of inflammatory bowel disease therapy to patients and families. *Curr Opin Pediatr.* 2017;29(5):572–577.

143. What pharmacologic therapies are used in the treatment of UC and CD?

Targeted treatments, including *biologic therapies,* have become much more prominent. Anti–tumor necrosis factor alpha (anti-TNF) antibodies, such as infliximab and adalimumab, have affected clinical outcomes by effectively achieving clinical remission and mucosal healing, treating perianal disease, and improving bone mineral density and growth. A recent prospective cohort study of CD demonstrated an association of early use of anti-TNF therapy and decreased likelihood of developing penetrating complications of the disease, but did not affect stricturing complications, which may require surgical intervention. Vedolizumab, a humanized anti-$\alpha 4\beta 7$ integrin monoclonal antibody that specifically inhibits T-cell migration in the GI tract, has shown modest improvement in clinical response and remission in adults, and observational studies have demonstrated similar responses in children.

Steroids, including prednisone, have previously been long-standing therapeutic options, but the risks from systemic immunosuppression, secondary adrenal insufficiency, and bone and cosmetic side effects have shifted the treatment paradigm toward steroid-sparing agents such as biologics. *5-Aminosalicyclic acid medications* are locally active anti-inflammatory agents that topically treat intestinal mucosa and are effective oral and rectal treatments for mild UC. *Antibiotics* to treat intestinal dysbiosis, including metronidazole, ciprofloxacin, and rifaximin, can be part of the therapeutic approach for IBD, but are primarily used for perianal disease or intra-abdominal abscesses in complicated CD. *Enteral nutritional therapy,* consuming 80% to 90% of all caloric intake by formula, is an effective steroid-sparing dietary therapy that induces remission and mucosal healing. Finally, *immunomodulators,* including thiopurines, are a long-standing option that effectively maintain remission in refractory, steroid-dependent CD, but the long-term safety profile has revealed a slightly increased risk for lymphoma in the patients exposed to thiopurines. *Dual therapy* that constitutes an immunomodulator such as methotrexate or thiopurine in addition to a biologic has been used for severe or refractory cases of IBD or to prevent antibody formation to biologic therapy that could render it ineffective.

Conrad MA, Rosh JR. Pediatric inflammatory bowel disease. *Pediatr Clin North Am.* 2017;64(3):577–591.
Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet.* 2017;389(10080):1710–1718.
Conrad MA, Stein R, Maxwell EC, et al. Vedolizumab therapy in severe pediatric inflammatory bowel disease. *Inflamm Bowel Dis.* 2016; 22(10):2425–2431.

144. In a child who has been diagnosed with CD, what are potential long-term complications?

- **Severe perianal disease** can be a debilitating complication. More prevalent in patients with CD, it may range from simple skin tags to the development of perianal abscesses or fistulas.
- **Enteroenteral fistulas** may occur and "short-circuit" the absorptive process. The thickened bowel may obstruct or perforate, thus requiring operation. The recurrence rate is high after surgery, repeated operations are often necessary, and short bowel syndrome may result. In many cases, a permanent ostomy is placed, although pouch construction and continent ileostomies have become more common.
- **Growth retardation and delayed puberty** are seen extensively in patients with pediatric CD. The insidious onset may result in several years of linear growth failure before the correct diagnosis is made. With epiphyseal closure, linear growth is terminated, and short adult stature will be permanent.
- **Decrease in bone mineralization** *(osteopenia)* is a more commonly recognized complication of CD, secondary to growth failure and malnutrition, disease activity, and the toxic effect of corticosteroids. All patients should have a bone densitometry scan to assess for this complication. Treatment includes increased weight-bearing activity, correction of nutritional deficits, vitamin D and calcium supplementation, and more aggressive medical treatment of disease.
- **Hepatic complications** of IBD include chronic active hepatitis and sclerosing cholangitis, which may require liver transplantation.
- **Nephrolithiasis** may occur in patients with resections or steatorrhea as a result of the increased intestinal absorption of oxalate.
- **Chronic reactive and restrictive pulmonary disease** has been noted.
- **Arthralgias** are common, but destructive joint disease is uncommon.

KEY POINTS: INFLAMMATORY BOWEL DISEASE

1. UC is limited to the superficial mucosa of the large intestine, always involves the rectum, and demonstrates no skip lesions.
2. CD can occur anywhere in the GI tract (from the mouth to the anus) and demonstrates transmural inflammation with skip lesions; noncaseating granulomas may be found on microscopic pathology. The transmural inflammation can result in the formation of abscesses or fistulas.
3. Potential long-term complications of IBD include chronic growth failure, abscesses, fistulas, nephrolithiasis, and osteopenia.
4. Surgery can be curative for UC, but the incidence of postoperative recurrence is high in CD.

145. Are children with IBD at increased risk for malignancy?

The risk for malignancy depends both on the disease and its duration. After 10 years of UC, the risk rises dramatically (1% to 2% increased incidence of malignancy per year). The risk is thought to be higher in patients with pancolitis compared with those with limited left-sided disease. The carcinomas associated with UC are often poorly differentiated and metastasize early; they have a poorer prognosis and are more difficult to identify by radiographic and colonoscopic examinations. Most authors indicate that carcinoma of the bowel is much less common among patients with CD, although this has been disputed. The risk for lymphoma is increased in patients with CD. Immunosuppressive (e.g., 6-mercaptopurine) and biologic (e.g., infliximab) therapy may also increase the risk for neoplasia. In one prospective study of long-term outcomes of pediatric-onset IBD with >24,000 patient-years of follow-up, 15 patients developed a malignancy and 5 patients developed hemophagocytic lymphohistiocytosis (HLH). There was not an increased risk for malignancy or HLH in those who were infliximab-exposed compared with those unexposed. The majority of the affected subjects did, however, have thiopurine exposure.

Hyams JS, Dubinsky MC, Baldassano RN, et al. Infliximab is not associated with increased risk of malignancy or hemophagocytic lymphohistiocytosis in pediatric patients with inflammatory bowel disease. *Gastroenterol.* 2017;152(8):1901–1914.

146. When is surgery indicated for children with IBD?

See Table 7.10.

Table 7.10 Indications for Surgery for Children With IBD

CROHN DISEASE	ULCERATIVE COLITIS
Perforation with abscess formation Obstruction with or without stenosis Uncontrolled massive bleeding Draining fistulas and sinuses Toxic megacolon Growth failure in patients with localized areas of resectable disease	*Urgent:* Hemorrhage Perforation Toxic megacolon Acute fulminant colitis unresponsive to maximal medical therapy *Elective:* Chronic disease with recurrent severe exacerbations Continuous incapacitating disease despite adequate medical treatment Growth retardation with pubertal delay Disease of >10 years' duration with evidence of epithelial dysplasia

From Hofley PM, Piccoli DA. Inflammatory bowel disease in children. *Med Clin North Am.* 1994;78(6):1293-1295.

LIPID DISORDERS

147. How are dyslipidemias defined?

Dyslipidemias involve abnormalities of the lipoproteins, which comprise the various types of cholesterol (see question 149) and triglycerides. Normative values for lipoproteins have been published based on a series of fasting lipoprotein profiles involving over 22,000 children (up to age 19 years). There are variations by age and sex.

Expert Panel on Integrated Guidelines. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics.* 2011;128(Suppl 5):S213.

148. What are the cutoffs for abnormal lipid levels?

See Table 7.11.

Table 7.11 Lipid Levels in Children and Adolescents

CATEGORY	ACCEPTABLE mg/dL	BORDERLINE mg/dL	HIGH mg/dL	LOW mg/dL
TC	<170	170-199	≥200	
LDL-c	<110	110-129	≥130	
Non HDL-c	<120	120-144	≥145	
TG				
0-9 yr	<75	75-99	≥100	
10-19 yr	<90	90-129	≥130	
HDL-c	>45	40-45		<40

HDL-c, high-density lipoprotein cholesterol; *LDL-c,* low-density lipoprotein cholesterol; *TC,* total cholesterol; *TG,* triglycerides.

149. What are the different types of cholesterol?

- **Triglycerides:** the major form of fat in the body
- **LDL:** low-density lipoprotein; the "bad" cholesterol; formed from very low-density lipoprotein (VLDL) or chylomicrons; saturated and trans fats increase LDL; major carrier of cholesterol *into* the body tissues
- **HDL:** high-density lipoprotein; "good" cholesterol; synthesized in the liver and gut; major carrier of cholesterol *away* from the body tissues
- **VLDL:** made by the liver; high in triglycerides
- **Chylomicrons:** transport dietary fat from intestines to liver and adipose tissues; high in triglycerides
- **Non-HDL (total cholesterol – HDL):** can be used if a nonfasting lipid profile is obtained or if triglycerides are >400

150. Why is the promotion of cardiovascular health and the identification of specific risk factors important in *pediatric* medicine?

- Atherosclerotic changes originate in childhood.
- Risk factors for the development of atherosclerosis can be identified in childhood.
- The progression of atherosclerosis relates to the number and intensity of these risk factors.
- Risk factors track from childhood to the adult years.
- Interventions exist for the management of identified risk factors.

Expert Panel on Integrated Guidelines. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics.* 2011;128(Suppl 5):S217.

151. What are the NHLBI screening guidelines for lipids?

Evidence-based guidelines from an expert panel from the National Heart, Lung and Blood Institute (NHLBI) include the following:

- **Birth to 2 years:** No lipid screening is recommended.
- **2 to 8 years:** No universal screening is recommended unless there are risk factors for cardiovascular disease (see later).
- **9 to 11 years:** Universal screening with nonfasting lipid panel is recommended.
- **12 to 16 years:** No routine screening is recommended unless there are *risk factors* for cardiovascular disease (see later). Universal lipid screening is not recommended in this age group because of decreased sensitivity and specificity for predicting adult values, particularly LDL.
- **17 to 19 years:** Universal screening is recommended once in this age group with a nonfasting or fasting lipid profile; repeat in 2 weeks to 3 months if abnormal.

Risk factors: parent with total cholesterol $\geq$240 mg/dL, early heart disease in a first- or second-degree relative, diabetes (type 1 or 2), hypertension, body mass index (BMI) greater than 95th percentile, smokes cigarettes, kidney disease, heart disease, chronic inflammatory disease, or HIV infection

152. What is a primary controversy in lipid screening in children?

There is significant debate on whether screening should be **universal or selective**. Proponents of universal screening insist that relying on the use of risk factors alone, such as a positive family history of premature cardiovascular disease, is an insensitive predictor and may miss 30% to 60% of children with dyslipidemia. Opponents of universal screening argue that the long-term benefits and outcomes of early identification of dyslipidemia are unknown, as are the use of potentially harmful medications (e.g., cholesterol-lowering agents such as statins) for what could be large numbers of children and adolescents. NHLBI recommendations (see question 151), which are endorsed by the AAP, use a combined approach of universal and selective screening.

Smith AJ, Turner EL, Kinra S. Universal cholesterol screening in childhood: a systematic review. *Acad Pediatr.* 2016;16(8):716–725.

153. What are the American Heart Association dietary recommendations for all children older than 2 years?

- Balance dietary calories with physical activity to maintain normal growth.
- Engage in 60 minutes of moderate to vigorous play or physical activity daily.
- Eat vegetables and fruit daily, limit juice intake.
- Use vegetable oils and soft margarines low in saturated fat and *trans* fatty acids instead of butter or most other animal fats in the diet.
- Eat whole-grain breads and cereals rather than refined-grain products.
- Reduce the intake of sugar-sweetened beverages and foods.
- Use nonfat (skim) or low-fat milk and dairy products daily.
- Eat more fish, especially oily fish, broiled or baked.
- Reduce salt intake, including salt from processed foods.

American Heart Association. Dietary recommendations for children and adolescents: a guide for practitioners. *Pediatrics.* 2006;117: 544–559.

154. How are the primary genetic hyperlipidemias classified?

See Table 7.12.

Table 7.12 Classification of Primary Genetic Hyperlipidemias

FREDERICKSON TYPE	LIPIDS INCREASED	LIPOPROTEINS INCREASED	PREVALENCE	CLINICAL FINDINGS
I	Triglyceride	Chylomicrons	Very rare	Eruptive xanthomas, pancreatitis, recurrent abdominal pain, lipemia retinalis, hepatosplenomegaly
IIa	Cholesterol	LDL	Common	Tendon xanthomas, PVD
IIb	Cholesterol, triglyceride	LDL + VLDL	Common	PVD, no xanthomas
III	Cholesterol, triglyceride	VLDL remnants (IDL)	Rare	PVD, yellow palm creases
IV	Triglyceride	VLDL	Uncommon	PVD, xanthomas, hyperglycemia
V	Triglyceride, cholesterol	VLDL + chylomicrons	Very rare	Pancreatitis, lipemia retinalis, xanthomas, hyperglycemia

IDL, Intermediate-density lipoprotein; *LDL*, low-density lipoprotein; *PVD*, peripheral vascular disease; *VLDL*, very low-density lipoprotein.

155. What is the most common hyperlipidemia in childhood?

Familial hypercholesterolemia, type IIA, with elevated cholesterol and LDL. This condition results from a lack of functional LDL receptors on cell membranes as a result of various mutations. When LDL cannot attach and release cholesterol to the cell, feedback suppression of hydroxymethylglutaryl coenzyme A reductase (the rate-limiting enzyme of cholesterol synthesis) does not occur, and cholesterol synthesis continues excessively. In the homozygous form of type IIa, xanthomas may appear before the age of 10 years and vascular disease before the age of 20 years. However, the homozygous form is very rare, with an incidence of 1 in 1,000,000 births. The heterozygous variety has a much higher incidence of 1 in 500, but it is less likely to produce clinical manifestations in children.

MALABSORPTION

156. What are the most useful stool tests for diagnosing fat malabsorption?

Measurement of 72-hour fecal fat is the gold-standard test for fat malabsorption. The patient must ingest a high-fat diet for 3 to 5 days (100 g daily for adults), and all stool is collected for the final 72 hours. A complete and accurate dietary history should be obtained concomitantly so the coefficient of fat absorption can be calculated. Steatorrhea is present if more than 7% of dietary fat is malabsorbed. In normal infants, up to 15% of fat can be malabsorbed. Other tests include Sudan staining of stool for fat globules (a qualitative test that, if positive, indicates gross steatorrhea), the steatocrit (percentage of fecal fat in a centrifuged stool sample), and monitoring absorbed lipids after a standardized meal.

157. What stool test is most useful for diagnosing GI protein loss?

Fecal α_1-antitrypsin measurement is the most useful stool marker of protein malabsorption. It is important to concomitantly measure serum α_1-antitrypsin to ensure that the patient does not have α_1-antitrypsin deficiency, which could result in a false-negative stool study.

158. What is primary lactose intolerance?

In more than 50% of the population, beginning at the age of 5 years, lactase levels decline progressively after having been normal in infancy. These levels decline at different rates for different people depending on their genetics. Most adults with primary lactose intolerance have lactase levels of about 10% of those seen during infancy. Symptoms of lactose intolerance (e.g., bloating, nausea, cramps, diarrhea after dairy foods) may develop if excessive lactose loads are ingested.

159. What conditions produce secondary lactose intolerance?

Any disorder that alters the mucosa of the proximal small intestine may result in secondary lactose intolerance. For this reason, the lactose tolerance test can be used as a screening test for intestinal integrity, although this has the disadvantage of concomitantly identifying all primary lactose malabsorbers. Although a combination of factors is present in many disease processes, secondary lactose intolerance can be organized into lesions of the microsurface, total surface, transit time, and site of bacterial colonization in the small bowel.

Microvillus and brush border:
- Postenteritis
- Bacterial overgrowth
- Inflammatory lesions (CD)

Level of the villus:
- Celiac disease
- Allergic enteropathy
- Eosinophilic gastroenteropathy

Bulk intestinal surface area:
- Short bowel syndrome

Altered transit with early lactose entry into colon:
- Hyperthyroidism
- Dumping syndromes
- Enteroenteral fistulas

160. How is lactose intolerance diagnosed?

The most common noninvasive method of diagnosing lactose intolerance is a **breath hydrogen test**. The fasted patient is fed 2 g/kg (up to 25 g) of lactose, and end-expired air is collected every 15 minutes for the next 2 to 3 hours for the purpose of measuring hydrogen concentration. Fermentation of carbohydrate by bacteria in the colon results in hydrogen expiration after lactose ingestion. A peak hydrogen level of 20 parts per million above the baseline after about 60 minutes in concert with a symptomatic response is considered a positive test. Because of the need for colonic bacteria to ferment carbohydrate and produce hydrogen gas, it is important that the patient not receive antibiotics immediately before the test.

Direct measurement of lactase levels, as well as the other disaccharidases, can be obtained by biopsy of the duodenum or jejunum during upper endoscopy.

Ugidos-Rodríguez S, Matallana-González MC, Sánchez-Mata MC. Lactose malabsorption and intolerance: a review. *Food Funct.* 2018; 9(8):4056–4068.

Heyman MB. Lactose intolerance in infants, children and adolescents. *Pediatrics.* 2006;118(3):1279–1286.

161. What is gluten?

After starch has been extracted from wheat flour, *gluten* is the residue that remains. This residue is made up of multiple proteins that are distinguished by their solubility and extraction properties. For example, the alcohol-soluble fraction of wheat gluten is wheat gliadin. It is this protein component that is primarily responsible for the mucosal injury that occurs in the small bowel in patients with celiac disease. The alcohol-soluble components of barley and rye are also harmful in the context of celiac disease.

162. What classic clinical features suggest celiac disease?

Gluten-sensitive enteropathy (celiac disease) is a relatively common cause of severe diarrhea and malabsorption in infants and children. The classic presentation of celiac disease is a 9- to 24-month-old child with FTT, diarrhea, abdominal distention, muscle wasting, and hypotonia. After several months of diarrhea, growth slows; weight typically decreases before height. Often, these children become irritable and depressed and display poor intake and symptoms of carbohydrate malabsorption. Vomiting is less common. On examination, the growth defect and distention can be striking. There may be a generalized lack of subcutaneous fat, with wasting of the buttocks, shoulder girdle, and thighs. Edema, rickets, and clubbing may also be seen. Many patients with celiac disease, however, have a more subtle presentation rather than the classic constellation of symptoms and can present at an older age.

Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *Lancet.* 2018;391(10115):70–81.

163. With which genetic conditions is celiac disease closely associated?

Celiac disease is more common in children with **Down syndrome** (5% to 12%), **Turner syndrome** (4% to 8%), **and Williams syndrome** (8% to 9.5%) than it is in the general population.

Thomas PC, Tighe MP, Beattie RM. Coeliac disease in children. *BMJ.* 2018;363:k3932.

Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr.* 2012;54(4):136–160.

164. What are possible extraintestinal manifestations of celiac disease?

- Dermatitis herpetiformis
- Iron-deficiency anemia (unresponsive to treatment with oral iron supplements)
- Arthritis and arthralgia
- Dental enamel hypoplasia

- Chronic hepatitis
- Osteopenia and osteoporosis
- Pubertal delay
- Short stature
- Lymphoma

Thomas PC, Tighe MP, Beattie RM. Coeliac disease in children. *BMJ.* 2018;363:k3932.
Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in the presentation of celiac disease. *Arch Pediatr Adolesc Med.* 2008;162(2):164–168.

165. What is the appropriate screening test for celiac disease?

Anti–tissue transglutaminase (TTG), immunoglobulin A (IgA), and **anti–endomysial (EMA) IgA antibodies** have been demonstrated to be highly sensitive and specific for celiac disease. Because of the low cost, ease of test performance, and reliability, *TTG* is currently recommended for initial screening of celiac disease. Antigliadin antibodies are not as sensitive or specific for celiac disease and are currently not recommended as first-line screening. Selective IgA deficiency is the most common primary immunodeficiency in Western countries, with a prevalence of 1.5 to 2.5 per 1000, and is even more common in patients with celiac disease. Therefore a quantitative total IgA level should be included when measuring IgA antibodies for celiac disease.

Tran TH. Advances in pediatric celiac disease. *Curr Opin Pediatr.* 2014;26(5):585–589.

166. What is the definitive way to diagnose celiac disease?

Definitive diagnosis of celiac disease requires **multiple small bowel biopsies via upper endoscopy** while the patient is on a gluten-containing diet. Intestinal biopsies obtained on gluten may show a number of abnormalities, including villous atrophy, elongated crypts, increased crypt mitoses, increased intraepithelial lymphocytes, plasma cell infiltrate in lamina propria, absence of brush border, and disorganization and flattening of the columnar epithelium ("villous blunting"). These abnormalities should resolve fully with repeat biopsies after a strict gluten-free diet. European guidelines have recommended that the need for confirmatory biopsy can be omitted in children with clear symptoms of celiac disease, with high levels of transglutaminase antibody, and with positive human leukocyte antigen (HLA) typing. Celiac disease is strongly associated with HLA-DQ types 2 and 8.

Reilly NR, Husby S, Sanders DS, Green PHR. Coeliac disease: to biopsy or not? *Nat Rev Gastroenterol Hepatol.* 2018;15(1):60-66.
Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr.* 2012;54(4):136–160.

167. What is the mainstay of treatment for celiac disease?

A strict **gluten-free diet** needs to be followed throughout life, although nearly one in four patients continues to experience GI symptoms. Gluten-free diets should be without wheat, barley, and rye. Upon initial diagnosis, most recommend avoiding oats because of contamination, but eventually most patients with celiac can tolerate oats. Good substitutions are rice and corn flour products. Care must be taken to avoid nutrient, vitamin, and mineral deficiencies or excesses.

Dennis M, Lee AR, McCarthy T. Nutritional considerations of the gluten-free diet. *Gastroenterol Clin North Am.* 2019;48(1):53–72.

NUTRITION

168. What are various requirements for protein, fat, and carbohydrates?

Protein should account for 7% to 15% of caloric intake and should include a balance of the 11 essential amino acids. Protein requirements range from 0.7 to 2.5 g/kg per day. *Fats* should provide 30% to 50% of caloric intake. Although most of these calories are derived from long-chain triglycerides, sterols, medium-chain triglycerides, and fatty acids may be important in certain diets. Linoleic acid and arachidonic acid are essential for tissue membrane synthesis, and about 3% of intake must be composed of these triglycerides. The remaining 50% to 60% of calories should come from *carbohydrates*. About half of these are contributed by monosaccharides and disaccharides (e.g., sucrose, lactose) and the remainder by starches.

169. If recommended caloric intakes are maintained, what is normal daily weight gain of young children?

See Table 7.13.

Table 7.13 Normal Daily Weight Gain in Young Children*

AGE	WEIGHT GAIN RECOMMENDED (g)	CALORIC INTAKE (kcal/kg/day)
0-3 mo	26-31	100-120
3-6 mo	17-18	105-115
6-9 mo	12-13	100-105
9-12 mo	9	100-105
1-3 yr	7-9	100
4-6 yr	6	90

*It should be noted that when babies are primarily breastfed, growth during months 3 to 18 is less than that indicated by the table. On average, breastfed babies gain 0.65 kg less than formula-fed infants during the first year of life.

Data from Dewey KG, Heinig MJ, Nommsen LA, et al. Growth of breast-fed and formula-fed infants from 0 to 18 months: the DARLING Study. *Pediatrics*. 1992;89:1035-1041; and National Research Council, Food and Nutrition Board. *Recommended Daily Allowances*. Washington, DC: National Academy of Sciences; 1989.

170. What are the recommended bottle feedings by age?

See Table 7.14.

Table 7.14 Recommended Bottle Feedings by Age

AGE	NUMBER OF FEEDINGS	FLUID OUNCES PER FEEDING
Birth-1 wk	6-10	1-3
1 wk-1 mo	7-8	2-4
1-3 mo	5-7	4-6
3-6 mo	4-5	6-7
6-9 mo	3-4	7-8

171. Why should whole cow milk not be introduced until 1 year of age?

Introduction of whole cow milk to infants <1 year of age is known to be detrimental. It is associated with **iron-deficiency anemia** because of its low iron content and occult intestinal blood loss, which occurs in 40% of normal young infants being fed cow milk. Early use of whole milk may contribute to weight acceleration and the development of **overweight/obesity**.

172. Why is honey not recommended for infants during the first year of life?

Honey has been associated with infantile botulism, as have some commercial corn syrups. *Clostridium botulinum* spores contaminate the honey and are ingested. More commonly, spores are dispersed from the soil of endemic areas. In infants, intestinal colonization and multiplication of the organism may result in toxin production and lead to symptoms of constipation, listlessness, and weakness.

173. How is nutritional status objectively assessed in children?

- **Growth chart:** Anthropometric data give an estimate of the height, weight, and head circumference of a child compared with a population standard. A change in the child's percentile for age over months may signify the presence of a nutritional problem or systemic disease.
- **Compare actual with ideal body weight** (average weight-for-height age): The ideal body weight is determined by plotting the child's height on the 50th percentile and recording the corresponding age. The 50th percentile weight for that age is obtained, and this ideal body weight is divided by the actual weight. The result is expressed as a percentage—the percentage of ideal body weight—that gives a better stratification of patients with significant malnutrition. An ideal body weight percentage of more than 120% is obese, 110% to 120% is overweight, 90% to 110% is normal, 80% to 90% is mild wasting, 70% to 80% is moderate wasting, and less than 70% is severe wasting.
- **Measurement of midarm circumference:** This provides information about the subcutaneous fat stores, and the midarm-muscle circumference (calculated from the triceps skinfold thickness) estimates the somatic protein or muscle mass. In newborns, the ratio of the midarm circumference to head circumference is used as a marker of intrauterine nutrition.

- **Laboratory assessment:** Vitamin and mineral status can be directly assayed. Measurements of albumin (half-life, 14 to 20 days), transferrin (half-life, 8 to 10 days), and prealbumin (half-life, 2 to 3 days) can provide information about protein synthesis, but each may be affected by certain diseases. The ratio of albumin to globulin may decrease in patients with protein malnutrition.

174. What features on examination of the scalp, eyes, and mouth suggest problems of malnutrition?

See Table 7.15.

Table 7.15 Effects of Malnutrition on Scalp, Eyes, and Mouth

CLINICAL SIGN	NUTRIENT DEFICIENCY
Epithelial	
Skin	
Xerosis, dry scaling	Essential fatty acids
Hyperkeratosis, plaques around hair follicles	Vitamin A
Ecchymoses, petechiae	Vitamin K
Hair	
Easily plucked, dyspigmented, lackluster	Protein calorie
Mouth, Lips, and Tongue	
Angular stomatitis (inflammation at corners of the mouth)	B_2 (riboflavin)
Cheilosis (reddened lips with fissures at angles)	B_2, B_6 (pyridoxine)
Glossitis (inflammation of tongue)	B_6, B_3 (niacin), B_2
Magenta tongue	B_2
Edema of tongue, tongue fissures	B_3
Spongy, bleeding gums	Vitamin C
Ocular	
Conjunctival pallor due to anemia	Vitamin E (premature infants), iron, folic acid, B_{12}, copper
Bitot spots (grayish, yellow, or white foamy spots on the whites of the eyes)	Vitamin A

175. How do marasmus and kwashiorkor differ clinically?

- *Kwashiorkor* is edematous malnutrition as a result of low serum oncotic pressure. The low serum proteins result from a disproportionately low protein intake compared with the overall caloric intake. These children appear replete of fat, but they have dependent edema, hyperkeratosis, and atrophic hair and skin. They generally have severe anorexia, diarrhea, and frequent infections, and they may have cardiac failure.
- *Marasmus* is severe nonedematous malnutrition caused by a mixed deficiency of both protein and calories. Serum protein and albumin levels are usually normal, but there is a marked decrease in muscle mass and adipose tissue. Signs are similar to those noted in hypothyroid children, with cold intolerance, listlessness, thin sparse hair, dry skin with decreased turgor, and hypotonia. Diarrhea, anorexia, vomiting, and recurrent infections may be noted.

176. What vitamins and minerals are often deficient in strict vegans and some vegetarians?

Vitamin B_{12}, iron, calcium, and zinc.

The groups most at risk are infants, children, and pregnant and lactating women. Semi-vegetarian diets rarely lead to such deficiencies.

PANCREATIC DISEASE

177. What are the possible causes of pancreatitis in children?

In adults, the majority of cases of pancreatitis arise from gallstones or alcohol. In children, there is a much greater diversity in etiology.

- *33%:* **Systemic disorders** (sepsis and shock, vasculitis)
- *13% to 34%:* **Idiopathic**
- *10% to 40%:* **Trauma** (motor vehicle accidents, sports injuries, accidental falls, child abuse)
- *10% to 30%:* **Biliary disease** (gallstones, sludge)

- *<25%:* **Medications** (valproic acid, L-asparaginase, prednisone, 6-mercaptopurine)
- *<10%:* **Infections** (various viral, including mumps)
- *5% to 8%:* **Hereditary** (genetic mutations)
- *2% to 7%:* **Metabolic disorders** (diabetic ketoacidosis [DKA], hypertriglyceridemia, hypercalcemia)
- *<3%:* **Anatomic and structural anomalies** (pancreatic divisum, duct anomalies, sphincter of Oddi dysfunction)

Sellers ZM, Abu-El-Haija M, Husain SZ, Morinville V. New management guidelines for both children and adults with acute pancreatitis. *Gastroenterology.* 2018;155(1):234–235.

Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. *J Pediatr.* 2015;166(4):890–896.

Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? *J Pediatr Gastroenterol Nutr.* 2011;52:262–270.

178. What is the typical presentation of acute pancreatitis in children?

In children >3 years of age, the most common symptom is **abdominal pain**, which occurs in 80% to 95%. Pain is typically epigastric in location. Radiation to the back is uncommon. Nausea or vomiting occurs in 40% to 80%. Abdominal distention is also common. Infants and toddlers are less likely to complain of abdominal pain and nausea and are more likely to have fever.

Uc A, Husain SZ. Pancreatitis in children. *Gastroenterology.* 2019;156(7):1969–1978.

Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? *J Pediatr Gastroenterol Nutr.* 2011;52(3):262–270.

179. Which enzyme is a more sensitive marker of pancreatic injury in children: amylase or lipase?

There is no clear winner. In a compilation of pediatric studies, the sensitivity of the amylase test in diagnosing pancreatitis has ranged from 50% to 85%, whereas lipase was only marginally more sensitive than amylase in most studies. Amylase values rise 2 to 12 hours after the onset of pancreatitis; lipase values rise at 4 to 8 hours. Because only one or the other may be elevated in individual patients, both lipase and amylase should be measured in suspected pancreatitis.

Srinath AI, Lowe ME. Pediatric pancreatitis. *Pediatr Rev.* 2013;34(2):79–89.

Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? *J Pediatr Gastroenterol Nutr.* 2011;52(3):262–270.

180. What conditions may be associated with hyperamylasemia?

- **Pancreatic:** pancreatitis, pancreatic tumors, pancreatic duct obstruction, biliary obstruction, perforated ulcer, bowel obstruction, acute appendicitis, mesenteric ischemia, endoscopic retrograde cholangiopancreatogram (ERCP)
- **Salivary:** infections (mumps), trauma, salivary duct obstruction, lung cancer, ovarian tumors or cysts, prostate tumors, DKA
- **Mixed or unknown:** cystic fibrosis, renal insufficiency, pregnancy, cerebral edema, burns

181. What is the role of stool elastase measurement?

Measurement of fecal pancreatic elastase is a screen for **exocrine pancreatic insufficiency**, which can be a cause of fat malabsorption (e.g., cystic fibrosis). A decreased measurement of pancreatic elastase is associated with pancreatic insufficiency, although values can be falsely decreased when the sample is obtained from a diarrheal specimen.

182. What is the difference between exocrine pancreatic insufficiency and endocrine pancreatic dysfunction?

Endocrine glands release hormones directly into the bloodstream. *Exocrine* glands secrete products into ducts that lead toward the target tissue. The pancreas contains exocrine cells and endocrine cells in close proximity to one another. Islet dysfunction, in cases of chronic pancreatitis or cystic fibrosis, for example, can lead to dysfunction in both cell types. *Exocrine pancreatic insufficiency* is due to loss of enzymes of digestion released from exocrine cells, which results in malabsorption of fat, diarrhea, poor weight gain, and abdominal pain, among other symptoms. In addition to malabsorbing fat, fat-soluble vitamins (A, D, E, and K) are often poorly absorbed. *Endocrine cell dysfunction* is due to diminished secretion of insulin and glucagons, which can result in diabetes mellitus.

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SURGICAL ISSUES

183. What is the likely diagnosis for an infant with excessive secretions and choking episodes in whom a nasogastric tube cannot be passed into the stomach?

Esophageal atresia with tracheoesophageal fistula. This congenital anomaly is usually diagnosed during the newborn period, often when a chest radiograph reveals the intended nasogastric tube coiled in the upper esophageal pouch with the stomach distended with air. Treatment is surgical. The possible variations are shown in Fig. 7.12.

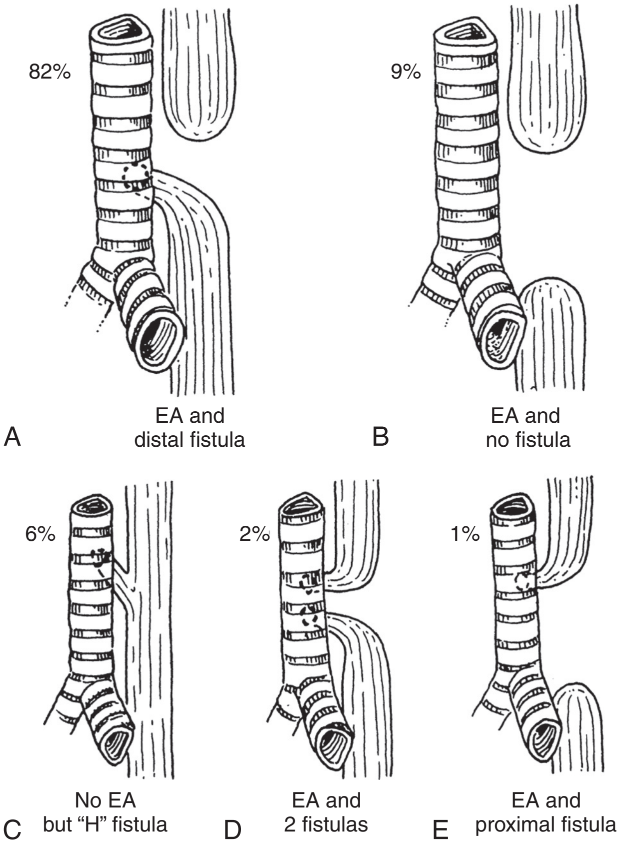

Fig. 7.12 (A) Esophageal atresia with distal esophageal communication with the tracheobronchial tree (most common type: 80%). (B) Esophageal atresia without a distal communication. (C) H-type fistulas between otherwise intact trachea and esophagus. (D) Esophageal atresia with both proximal and distal communication with the trachea. (E) Esophageal atresia with proximal communication. (From Blickman H, ed. *The Requisites: Pediatric Radiology*. 2nd ed. Philadelphia, PA: Mosby; 1998:93.)

184. What is the natural history of an umbilical hernia?

Most umbilical hernias smaller than 0.5 cm spontaneously close before a patient is 2 years old. Those between 0.5 and 1.5 cm take up to 4 years to close. If the umbilical hernia is larger than 2 cm, it may still close spontaneously, but may take up to 6 years or more to do so. Unlike an inguinal hernia, incarceration and strangulation are rare with an umbilical hernia.

Barreto L, Khan AR, Khanbhal M, et al. Umbilical hernia. *BMJ.* 2013;347:f4252.

185. Which umbilical hernias warrant surgical repair?

Because of the high probability of self-resolution, indications for surgery are controversial. Some authorities argue that a hernia larger than 1.5 cm at the age of 2 years warrants closure as a result of its likely persistence for years. Others argue that because the likelihood of incarceration is small for umbilical hernias, surgical closure is warranted before puberty only for persistent pain, history of incarceration, or associated psychological disturbances.

186. When should an infant with inguinal hernia have it electively repaired?

After the diagnosis of inguinal hernia is made, it should be repaired **as soon as possible**. In one large study of children with incarcerated hernia, 40% of patients had a known inguinal hernia before incarceration and 80% were awaiting elective repair. Eighty percent of the children with incarceration of a hernia were infants younger than 1 year. Delay of repair should be minimized, especially in this age group. Another study found that if an infant presents with an incarcerated hernia, subsequently reduced in the ED, the potential for recurrent incarceration during a waiting period is increased 12-fold.

Chen LE, Zamakhshary M, Foglia RP, et al. Impact of wait time on outcome for inguinal hernia repair in infants. *Pediatr Surg Int.* 2009;25(3):225–232.

Stylianos S, Jacir NN, Harris BH. Incarceration of inguinal hernia in infants prior to elective repair. *J Pediatr Surg.* 1993;28(4):582–583.

187. Does surgical repair of one hernia warrant intraoperative exploration for another on the opposite side?

This is a controversial topic. Many surgeons opt to have pediatric patients undergo exploration of the contralateral side during a hernia repair because 60% of infants will have a patent processus vaginalis on the opposite side. By age 2 years, approximately 10% of these become clinical hernias, although a large percentage do spontaneously obliterate before that time. Other surgeons feel the potential risk for contralateral exploration (e.g., injury to the vas deferens, testes, and ilioinguinal nerve) mandates a watchful waiting approach. Surveys of pediatric surgeons indicate persistent widespread practice variability.

Palmer LS. Hernias and hydroceles. *Pediatr Rev.* 2013;34(10):457–463.

Ron O, Eaton S, Pierro A. Systematic review of the risk of developing a metachronous contralateral inguinal hernia in children. *Br J Surg.* 2007;94(7):804–811.

188. What is the significance of green vomiting during the first 72 hours of life?

During the neonatal period, bilious vomiting should always be interpreted as a sign of potential intestinal obstruction possibly requiring surgical intervention. In one study of 45 infants with bilious vomiting, 20% had surgical conditions (e.g., malrotation, jejunal atresia, jejunal stenosis), 10% had nonsurgical obstruction (e.g., meconium plug, microcolon), and 70% had idiopathic vomiting that self-resolved. Plain radiographs frequently can be normal, particularly for malrotation, and thus falsely reassuring.

Williams H. Green for danger! Intestinal malrotation and volvulus. *Arch Dis Child Educ Pract Ed.* 2007;92(3):ep87–ep97.

Lilien LD, Srinivasan G, Pyati SP, et al. Green vomiting in the first 72 hours in normal infants. *Am J Dis Child.* 1986;140(7):662–664.

189. Why are children with malrotation at risk for intestinal obstruction?

Malrotation of the intestine is the result of the abnormal rotation of the intestine in the tenth week of gestation around the superior mesenteric artery. Arrest of this counterclockwise rotation may occur at any degree of rotation. The cecum is unattached and located in the upper abdomen. One consequence of improper fixation of the mesentery allows for a loop of intestine to twist around itself, which can result in a bowel obstruction *(volvulus)*. Additionally, abnormal tissue *(Ladd bands)* connects the abnormally located cecum to the abdominal wall and may create a duodenal obstruction (Fig. 7.13).

190. What are the clinical findings of malrotation and volvulus of the intestine?

The lesion may display as early as in utero as volvulus, or it may be asymptomatic throughout life. Infants may display intermittent vomiting or exhibit signs compatible with complete obstruction. Any infant with bilious vomiting should be considered emergent and requires careful evaluation for volvulus and other high-grade surgical obstructions. Recurrent abdominal pain, distention, or lower GI bleeding may result from intermittent volvulus. Full volvulus with arterial compromise results in intestinal necrosis, peritonitis, perforation, and an extremely high incidence of mortality. Because of the extensive nature of the lesion, postoperative short gut syndrome is present in many patients who require resection. An upper GI contrast study is the examination of choice when the diagnosis is suspected.

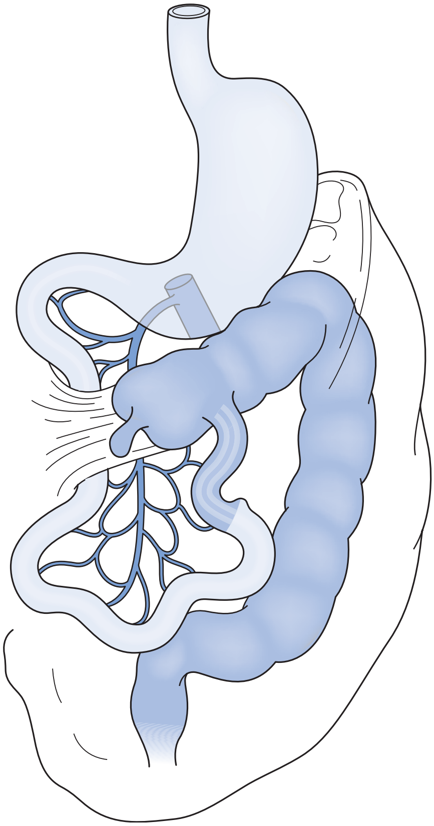

Fig. 7.13 Incomplete intestinal rotation. Ladd bands are seen attaching the cecum to the right posterior abdominal wall. The duodenum can become compressed and possibly obstructed. (From Holcombe GW, Murphy JP, Ostlie DJ. *Ashcraft's Pediatric Surgery.* 6th ed. Philadelphia, PA: Elsevier; 2014:430-438.)

191. In an asymptomatic child with an incidental finding of malrotation, is surgery indicated?

Because of the persistent possibility of acute volvulus and intestinal obstruction, surgery is always indicated when intestinal malrotation is diagnosed.

192. What is the most common cause of intestinal obstruction in young children?

Intussusception, which occurs when one portion of the bowel invaginates into a distal segment of bowel, is the most common cause of intestinal obstruction in young children. Intussusception usually occurs before the second year of life; half of all cases occur between the ages of 3 and 9 months.

193. In what settings should intussusception be suspected?

Colicky pain is seen in more than 80% of cases, but it may be absent. It typically lasts 15 to 30 minutes, and the baby usually sleeps between attacks. In about two-thirds of cases, there is blood in the stool (currant jelly stools). Other presenting symptoms include massive lower GI bleeding or blood streaking on the stools. The infant may appear quite toxic, dehydrated, or in shock; fever and tachycardia are common. A right lower quadrant mass may be palpable, or the area may feel surprisingly empty. Distention may accompany decreased bowel sounds.

194. How commonly does intussusception appear with the classic findings?

The classic triad of intussusception (colicky pain, vomiting, and passage of bloody stool) is the exception; overall, 80% of patients do not have this triad of symptoms. About 30% have blood in the stool, and this percentage may drop to about 15% if the abdominal pain was present for <12 hours. Palpation of a mass can suggest the diagnosis, but generally a high degree of suspicion is important. Delay in diagnosis is common.

Lochhead A, Jamjoom R, Ratnapalan S. Intussusception in children presenting to the emergency department. *Clin Pediatr.* 2013;52(11):1029–1033.

Klein EJ, Kapoor D, Shugerman RP. The diagnosis of intussusception. *Clin Pediatr.* 2004;43(4):343–347.

195. What causes intussusception?

Intussusception is caused by one proximal segment of the bowel being invaginated and progressively drawn caudad and encased by the lumen of distal bowel. This causes obstruction and may occlude the vascular supply of the bowel segment. There is commonly a lead point on the proximal bowel that initiates the process. Lead points have included juvenile polyps, lymphoid hyperplasia, hypertrophied Peyer patches, eosinophilic granuloma of the ileum, lymphoma, lymphosarcoma, leiomyosarcoma, leukemic infiltrate, duplication cysts, ectopic pancreas, Meckel diverticulum, hematoma, Henoch-Schönlein purpura, worms, foreign bodies, and appendicitis.

Waseem M, Rosenberg HK. Intussusception. *Pediatr Emerg Care.* 2008;24(11):793–800.

196. What is the most common type of intussusception?

Ileocolic intussusception (Fig. 7.14) is most common, and it is also the most common cause of intestinal obstruction during infancy. Cecocecal and colocolic intussusceptions are less common. Gastroduodenal intussusception is rare and is usually associated with a gastric mass lesion such as a polyp or a leiomyoma. Enteroenteral intussusception is seen after surgery and in patients with Henoch-Schönlein purpura.

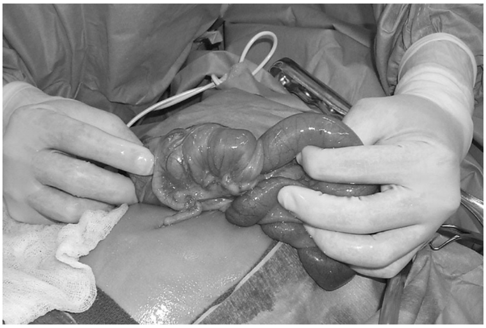

Fig. 7.14 Intraoperative appearance of ileocolic intussusception through the ileocecal valve. (From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 3rd ed. Philadelphia, PA: Saunders; 2016:717.)

197. How is intussusception diagnosed and treated?

Ultrasound is the standard study to make this diagnosis and has a role in the evaluation of reducibility, identification of a potential pathologic lead point, and exclusion of residual intussusception after enema. Previously, the diagnostic study of choice was a barium enema. Compared with barium enema, air enema is now considered to be a safer, faster, and more effective method of reduction with less radiation. In about three-quarters of cases, air enema under fixed hydrostatic pressure will reduce the intussusception. If this is unsuccessful, surgical reduction is necessary.

Edwards EA, Pigg N, Courtier J, et al. Intussusception: past, present and future. *Pediatr Radiol.* 2017;47(9):1101-1108.

Gluckman S, Karpelowsky J, Webster AC, McGee RG. Management for intussusception in children. *Cochrane Database Syst Rev.* 2017;6:CD006476.

198. How frequently does intussusception recur?

Overall recurrence rates for intussusception are about 13%. The recurrence rate during the first 24 hours is low, 2% to 4%, so the vast majority of recurrences will not be identified by overnight hospitalization.

Gray MP, Li S-H, Hoffman R, et al. Recurrence rates after intussusception enema reduction: a meta-analysis. *Pediatrics.* 2014;134(1):110–119.

199. Rotavirus vaccine and intussusception: How are they intertwined?

Rotashield, an oral rotavirus vaccine licensed in the United States in 1998, was suspended from use in 1999 when increased rates of intussusception were noted in association with it. Two newer rotavirus vaccines, RotaTeq (based on an attenuated bovine strain) and Rotarix (based on a human rotavirus serotype), were licensed in 2006 and 2008, respectively. International postlicensure studies and U.S. data have suggested a slightly increased risk for intussusception during the first 3 weeks after the first dose of both vaccines.

Soares-Weiser K, Bergman H, Henschke N, et al. Vaccines for preventing rotavirus diarrhea: vaccines in use. *Cochrane Database Syst Rev.* 2019;3:CD008521.

Kassim P, Eslick GD. Risk of intussusception following rotavirus vaccination: an evidence based meta-analysis of cohort and case-control studies. *Vaccine.* 2017;35(33):4276–4286.

200. Duodenal or jejunoileal atresia: Which is associated with other embryonic abnormalities?

- *Duodenal atresia* is caused by a persistence of the proliferative stage of gut development and a lack of secondary vacuolization and recanalization. It is associated with a high incidence of other early embryonic abnormalities. Extraintestinal anomalies occur in two-thirds of patients with this condition.
- *Jejunoileal atresia* occurs after the establishment of continuity and patency of intestinal lumen, as evidenced by distal meconium seen in these patients. The etiology is postulated to be a vascular accident, volvulus, or mechanical perforation. Jejunoileal atresias are usually not associated with any other systemic abnormality.

201. What is the classic radiographic finding in duodenal atresia?

The double bubble sign as swallowed air distends the stomach and the proximal duodenum (Fig. 7.15).

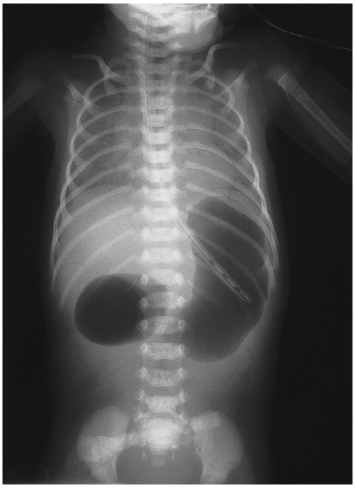

Fig. 7.15 Duodenal atresia. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis*. 5th ed. Philadelphia, PA: Mosby; 2007:637.)

202. What is the surgical procedure for biliary atresia?

The **Kasai procedure** (hepatoportoenterostomy). The remnants of the extrahepatic biliary tree are identified, and a cholangiogram is performed to verify the diagnosis. An intestinal limb (Roux-en-Y) is attached to drain bile from the porta hepatis.

203. Which is accompanied by more complications: High or low imperforate anus?

High-type imperforations. The distinction is based on whether the blind end of the terminal bowel or rectum ends above (high type) or below (low type) the level of the pelvic levator musculature. Patients with high-type imperforations will have ectopic fistulas (rectourinary, rectovaginal), urologic anomalies (hydronephrosis or double collecting system), and lumbosacral spine defects (sacral agenesis, hemivertebrae). The surgical repair in these patients is much more extensive, and future problems of incontinence, fecal impaction, and strictures are more likely.

204. What is the classic presentation of pyloric stenosis?

An infant 2 to 6 weeks of age has progressive, *nonbilious,* projectile vomiting leading to dehydration with hypochloremic, hypokalemic, metabolic alkalosis. On physical examination, a pyloric “olive” may be palpable, and peristaltic waves are visible.

205. How is pyloric stenosis diagnosed?

If the classic signs and symptoms are present in association with the typical blood chemistry findings (hypochloremia, hypokalemia, metabolic alkalosis) and a mass is palpated, the diagnosis can be made on **clinical** grounds. If the diagnosis is in doubt, **ultrasound** should be used to visualize the hypertrophic pyloric musculature (Fig. 7.16). **Upper GI contrast** studies demonstrate pyloric obstruction with the characteristic “string sign” and enlarged “shoulders” bordering the elongated and obstructed pyloric channel.

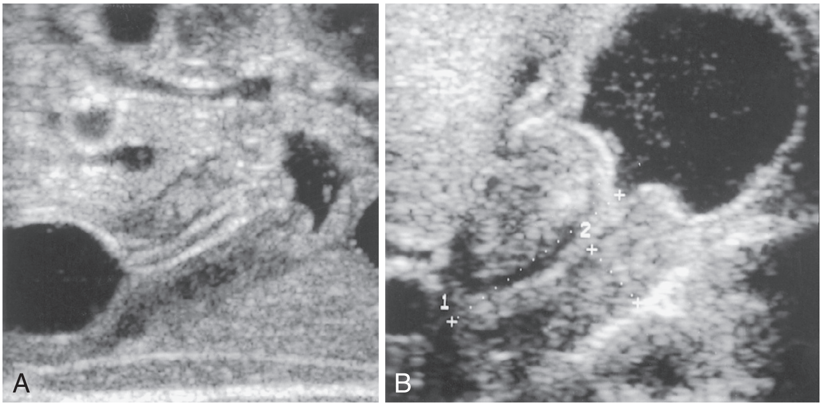

Fig. 7.16 (A) Ultrasound of pyloric stenosis. Note the elongated and curved pyloric channel with parallel walls and the thickened muscle with a "shoulder" projecting into the antrum. (B) Longitudinal sonograph of the pylorus in a patient with pyloric stenosis. *1,* canal length = 1.7 cm; *2,* muscle wall thickness = 0.6 cm. (From Glick PL, Pearl RH, Irish MS, Caty MG. *Pediatric Surgery Secrets*. Philadelphia, PA: Hanley & Belfus; 2001:203.)

206. In a patient with suspected pyloric stenosis, why is an acidic urine very worrisome?

As vomiting progresses in infants with pyloric stenosis, a worsening hypochloremic metabolic alkalosis develops. Multiple factors (e.g., volume depletion, elevated aldosterone levels) result in maximal renal efforts to reabsorb sodium. In the distal tubule, this is typically achieved by exchanging sodium for potassium and hydrogen. When total-body potassium levels are very low, hydrogen is preferentially exchanged, and a paradoxic aciduria develops (in the setting of an alkaline plasma). This acidic urine is an indication that intravascular volume expansion and electrolyte replenishment (especially chloride and potassium) are urgently needed.

Jobson M, Hall NJ. Contemporary management of pyloric stenosis. *Semin Pediatr Surg*. 2016;25(4):219–224.

207. What is the connection between pyloric stenosis and macrolide antibiotics?

The use of erythromycin during the first 2 weeks after birth is associated with an increased risk, up to 30-fold, for the development of pyloric stenosis. Azithromycin use increases the risk up to 8-fold. Use of erythromycin or azithromycin from 2 weeks to 4 months of age is also associated with an increased risk, albeit smaller. Speculation on a mechanism involves possible macrolide effects as a prokinetic agent on GI smooth muscle, which could cause spasm of the pyloric muscle.

Eberly MD, Eide MB, Thompson JL, Nylund CM. Azithromycin in early infancy and pyloric stenosis. *Pediatrics.* 2015;135(3):483–488.
Lund M, Pasternak B, Davidsen RB, et al. Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study. *BMJ.* 2014;348:1908–1918.

208. What is short bowel syndrome?

Short bowel syndrome results from extensive resection of the small intestine. Normally, most carbohydrates, proteins, fats, and vitamins are absorbed in the jejunum and the proximal ileum. The terminal ileum is responsible for the uptake of bile acids and vitamin B_{12}. Short bowel syndrome results in failure to thrive, malabsorption, diarrhea, vitamin deficiency, bacterial contamination, and gastric hypersecretion.

209. Why are infants with short bowel syndrome prone to renal calculi?

Chronic intestinal malabsorption results in an increase of intraluminal fatty acids, which saponify with dietary calcium. Thus nonabsorbable calcium oxalate does not form; excessive oxalate is absorbed, and hyperoxaluria with crystal formation results.

210. In extensive small bowel resection, how much is "too much"?

Infants who retain 20 cm of small bowel as measured from the ligament of Treitz can survive if the ileocecal valve is intact. If the ileocecal valve has been removed, the infant usually requires a minimum of 40 cm of bowel to survive. The importance of the ileocecal valve appears to relate to its ability to retard transit time and minimize bacterial contamination of the small intestine.

KEY POINTS: SURGICAL ISSUES

1. Bilious (dark green) emesis in a newborn is a true GI emergency; it is a sign of potential obstruction.
2. The classic triad of intussusception consists of the following: (1) colicky abdominal pain, (2) vomiting, and (3) bloody stools with mucus. However, it occurs in less than 20% of patients.
3. In patients younger than 2 years, intussusception is the most common abdominal emergency.
4. Pyloric stenosis typically presents with progressive, nonbilious, projectile vomiting and a hypochloremic, hypokalemic metabolic alkalosis in an infant between the ages of 2 and 6 weeks.
5. The classic picture of appendicitis is anorexia followed by pain, followed by nausea and vomiting, with subsequent localization of findings to the right lower quadrant. However, there is a large degree of variability, particularly in younger patients.

211. Appendicitis in children: Clinical, laboratory, or radiologic diagnosis?

The diagnosis of appendicitis has traditionally been a clinical one. The classic picture in children is a period of **anorexia followed by pain, nausea, and vomiting**. Abdominal pain begins periumbilically and then shifts after 4 to 6 hours to the right lower quadrant. Fever is low grade. Peritoneal signs are detected on examination. In unequivocal cases, experienced surgeons would argue that no laboratory tests are needed.

Laboratory studies have limited value in equivocal cases. White blood cell count of more than 18,000/mm^3 or a marked left shift is unusual in uncomplicated cases and suggests perforation or another diagnosis. The sensitivity and specificity of inflammatory markers (e.g., sed rate, C-reactive protein) have wide ranges in various studies. A urinalysis with many white blood cells suggests a urinary tract infection as the primary pathology, and hematuria suggests nephrolithiasis. In a postmenarchal adolescent female, a pregnancy test (urine β-human chorionic gonadotropin [HCG]) should be considered for evaluation of a possible ectopic pregnancy.

It is uncommon for children to undergo surgery for suspected appendicitis without imaging. CT has been considered the gold standard for diagnosis. However, in many centers with equivocal clinical findings for which imaging is indicated, ultrasound has been utilized as the initial imaging study. Ultrasound limits radiation, but is highly operator dependent. If the initial and/or repeat ultrasounds are nondiagnostic and a diagnosis remains in question, contrast-enhanced CT are obtained. Magnetic resonance imaging (MRI) is an option, but studies of its use in pediatric medicine are limited, and availability is primarily in pediatric centers due to issues of sedation and interpretation.

Mittal MK. Appendicitis: Role of MRI. *Pediatr Emerg Care.* 2019;35(1):63–66.
Rentea RM, Peter SDS, Snyder CL. Pediatric appendicitis: state of the art review. *Pediatr Surg Int.* 2017;33(3):269–283.
Aspelund G, Fingeret A, Gross E, et al. Ultrasonography/MRI versus CT for diagnosing appendicitis. *Pediatrics.* 2014;133:1–8.

212. How specific is the diagnosis of appendicitis if an appendicolith is noted on radiograph?

Although an appendicolith (or fecalith), a calcification within the appendiceal lumen, on radiographic studies (plain film or CT scan) is significantly associated with appendicitis, it is not sufficiently specific to be the sole basis for the diagnosis. On CT scanning, these can be noted in 65% of patients with appendicitis and in up to 15% of patients without appendicitis. The positive predictive value of finding an appendicolith is about 75%; in its absence, the negative predictive value is only 26%.

Lowe LH, Penney MW, Scheker LE, et al. Appendicolith revealed on CT in children with suspected appendicitis: how specific is it in the diagnosis of appendicitis? *AJR Am J Roentgenol.* 2000;175(4):981–984.

213. In children taken to surgery for suspected appendicitis, how often is perforation of the appendix present?

It depends to a large extent on the age of the child (and, of course, on the skill of the clinician). Unfortunately, as a result of the variable location of the appendix, the clinical presentation of pain in appendicitis is often very different from the classic case. The younger the child, the more difficult the diagnosis. In infants younger than 1 year, nearly 100% of patients who come to surgery have a perforation. Fortunately, appendicitis is rare in this age group because the appendiceal opening at the cecum is much larger than the tip, and obstruction is unusual. In children younger than 2 years, 70% to 80% are perforated; in those 5 years and younger, 50% are perforated. Particularly in younger children, a high index of suspicion is necessary, and rapid diagnosis is critical. If the onset of symptoms can be pinpointed (usually anorexia related to a meal), 10% of patients will have perforation during the first 24 hours, but more than 50% will perforate by 48 hours.

214. Should children with acute abdominal pain be given analgesia before a diagnosis?

This is a controversial question because of a long-held fear that treating the pain may mask the symptoms, change the physical findings, and potentially delay the diagnosis of a possible surgical problem. However, there is growing evidence that the use of opiate analgesia in patients, including children, with acute abdominal pain does not result in increased mortality or morbidity.

Bailey B, Bergeron S, Gravel J, et al. Efficacy and impact of intravenous morphine before surgical consultation in children with right lower quadrant pain suggestive of appendicitis: a randomized controlled trial. *J Pediatr.* 2007;50(4):371–378.

Ranji SR, Goldman LE, Simel DL, et al. Do opiates affect the clinical evaluation of patients with acute abdominal pain? *JAMA.* 2006; 296(14):1764–1774.

215. Is nonoperative management of acute appendicitis an option?

Although traditionally the standard of care for children with appendicitis has been an urgent appendectomy, there is increasing debate regarding whether some patients (pediatric and adult) with acute appendicitis, both uncomplicated and complicated, can be managed nonoperatively. This nonsurgical alternative is to treat patients with antibiotics alone while awaiting resolution of symptoms. There is the possibility of interval surgery in the future. In uncomplicated cases (i.e., unruptured appendicitis) for which surgery was deferred, studies have found high success rates (70% to 80% at 1 year) with limited complications or need for future appendectomy in select patients (e.g., symptoms <24 hours). In complicated appendicitis cases (e.g., phlegmon, perforation, intraperitoneal abscess), the choice is early appendectomy versus initial nonoperative management with 6 to 8 weeks of antibiotics followed by surgery at variable times. The debate is further accentuated by the availability of laparoscopic appendectomy, which shortens recovery times. Several multicenter studies are underway to investigate the safety and efficacy of a nonoperative approach and, in particular, which subset of patients with which inclusion criteria might benefit most from this approach.

Lopez JJ, Deans DJ, Minneci PC. Nonoperative management of appendicitis in children. *Curr Opin Pediatr.* 2017;29(3):358–362.

Gonzalez DO, Deans KJ, Minneci PC. Role of non-operative management in pediatric appendicitis. *Semin Pediatr Surg.* 2016;25(4):204–207.

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CHAPTER 8

GENETICS

Kwame Anyane-Yeboa, MD, Elaine M. Pereira, MD
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CLINICAL ISSUES

1. Which disorders with ethnic and racial predilections most commonly warrant maternal screening for carrier status?

See Table 8.1.

Table 8.1 Maternal Screening According to Ethnic and Racial Predilections

DISORDER	ETHNIC OR RACIAL GROUP	SCREENING TEST
Tay-Sachs disease	Ashkenazi Jewish, French, French Canadian	Decreased serum hexosaminidase A concentration, DNA studies
Familial dysautonomia	Ashkenazi Jewish	DNA
Gaucher disease	Ashkenazi Jewish	DNA
Canavan disease	Ashkenazi Jewish	DNA
Bloom syndrome	Ashkenazi Jewish	DNA
Fanconi anemia	Ashkenazi Jewish	DNA
Niemann-Pick disease (type A)	Ashkenazi Jewish	DNA
Mucolipidosis IV	Ashkenazi Jewish	DNA
Cystic fibrosis	Pan ethnic	DNA
Sickle cell anemia	Black, African, Mediterranean, Arab, Indian, Pakistani	Presence of sickling in hemolysate followed by confirmatory hemoglobin electrophoresis

DNA, Deoxyribonucleic acid.

2. Why are mitochondrial disorders transmitted from generation to generation by the mother and not the father?

Mitochondrial deoxyribonucleic acid (DNA) abnormalities (e.g., many cases of ragged red fiber myopathies) are passed on from the mother because mitochondria are present in the cytoplasm of the egg and not the sperm. Transmission to males or females is equally likely; however, expression is variable because mosaicism with normal and abnormal mitochondria in varying proportions is very common.

Gorman GS, Chinnery PF, DiMauro S, et al. Mitochondrial diseases. *Nat Rev Dis Primers*. 2016;2:16080.
McFarland R, Taylor RW, Turnbull DM. A neurological perspective on mitochondrial disease. *Lancet Neurol.* 2010;9(8):829–840.
Johns DR. Mitochondrial DNA and disease. *N Engl J Med.* 1995;333(10):638–644.

3. What is genetic imprinting?

Genetic imprinting is a genetic mechanism by which genes are selectively expressed from the maternal or paternal allele on a chromosome. As a consequence, depending on the gene, only the maternal or the paternal allele is expressed. The inactive allele is epigenetically marked by histone modification, DNA (cytosine) methylation, or both. The imprint is maintained throughout the life of the individual. However, imprints are erased during early development of the male and female germlines and then reset before germ cell maturation. Imprinted genes play crucial roles in growth, development, and tumor control. Imprinted genes can cause disease when the maternal/paternal gene that is usually expressed is mutated, silenced, or deleted. In humans about 50 genes are known to be imprinted. Classic examples of human diseases linked to imprinting defects are transient neonatal diabetes, Russell-Silver syndrome, Beckwith-Wiedemann syndrome, Prader-Willi syndrome, Angelman syndrome, and Albright hereditary osteodystrophy.

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Pediatrics & Neonatology Journals [Ahmed Manfy] on TELEGRAM

Mackay DJG, Temple IK. Human imprinting disorders: principles, practice, problems and progress. *Eur J Med Genet.* 2017;60(11):618–626.

Soellner L, Begemann M, Mackay DJ, et al. Recent advances in imprinting disorders. *Clin Genet.* 2017;91(1):3–13.

4. What is uniparental disomy?

Uniparental disomy occurs when a fetus receives two copies of a chromosome, or portions of a chromosome, from only one parent with no copies from the other parent. In most instances, this is not significant. However, the concept of genetic imprinting does have a role here. Because some essential genes undergo genetic imprinting, if a fetus lacks those imprinted genes from one parent, there can be a loss of gene function, which can lead to the diseases noted in question 3.

Yamazawa K, Ogata T, Ferguson-Smith AC. Uniparental disomy and human disease: an overview. *Am J Med Genet C Semin Med Genet.* 2010;154C(3):329–334.

5. What is the etiology of arthrogryposis congenita?

Arthrogryposis congenita (AC) refers to nonprogressive, congenital joint contractures (single or multiple) that generally result from lack of fetal movements in utero.

Any condition intrinsic to the fetus or secondary to environmental/maternal factors that decreases fetal movements can lead to arthrogryposis congenita. Decreased fetal movement leads to increased connective tissue around the joint(s), skin dimpling over the immobilized joint(s), and disuse atrophy of the muscles that mobilize the joint (Fig. 8.1). Etiologies include muscle disease, central nervous system (CNS) disorders, connective tissue disorders, maternal illness (e.g., myasthenia, myotonic dystrophy, hyperthermia [fever >39°C]), and a host of specific genetic disorders. Specific genetic conditions associated with arthrogryposis congenita are fetal akinesia syndrome, amyoplasia (classical arthrogryposis), distal arthrogryposis type 1, congenital contractural arachnodactyly (Beal syndrome), multiple pterygium syndromes, and cerebro-oculo-facial-skeletal syndrome (COFS). Inheritance varies depending on the specific type.

Hall JG. Arthrogryposis (multiple congenital contractures). Diagnostic approach to etiology, classification, genetics and general principles. *Eur J Med Gen.* 2014;57(8):464–472.

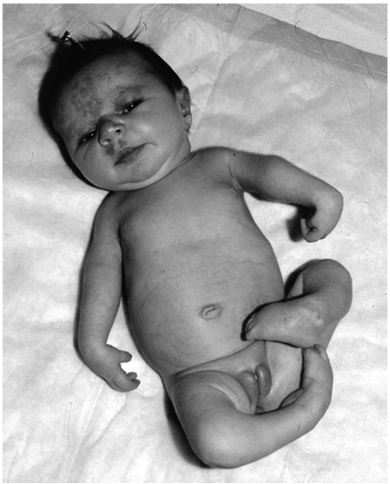

Fig. 8.1 A 1-month-old girl with the quadrimelic form of arthrogryposis. (From Staheli LT, Song KM. *Pediatric Orthopedic Secrets*. 3rd ed. Philadelphia, PA: Elsevier; 2007:494-498.)

6. How common are genetic causes of hearing loss in childhood?

Hearing loss significant enough to affect speech and language development affects 2 to 3 of every 1000 births in the United States. **About 50%** of cases are due to genetic causes. Inheritance can be autosomal dominant, recessive, X-linked, or mitochondrial. More than 400 genetic syndromes include hearing loss as a feature, including Waardenburg syndrome (pigmentary anomalies), Pendred syndrome (enlarged vestibular aqueduct), branchio-oto-renal syndrome (branchial arch and renal anomalies), Treacher-Collins syndrome, and Usher syndrome (retinitis pigmentosa).

Alford RL, Arnos KS, Fox M, et al. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. *Genet Med.* 2014;16(4):347–355.

7. What is the most common genetic mutation in infants with prelingual hearing loss?

Prelingual hearing loss is hearing loss detected before speech development. All congenital hearing loss, by definition, is prelingual. The ***GJB2*** **gene (gap junction β-2)** is the most common site for a mutation. In patients with congenital nonsyndromic deafness, about 75% are due to mutations in that gene. The *GJB2* gene encodes the protein connexin 26, which is critical for gap junctions between cochlear cells. Connexin mutations are usually autosomal recessive. Another mutation classified as 167delT is found exclusively in the Ashkenazi Jewish population.

Chan DK, Chang KW. GJB2-associated hearing loss: systematic review of worldwide prevalence, genotype, and auditory phenotype. *Laryngoscope.* 2014;124(2):e34–e53.

8. What are the genetic causes of microcephaly?

Microcephaly, defined as an occipital-frontal circumference below the third percentile or 3 standard deviations below the mean, can be associated with more than 500 genetic syndromes. Chromosome defects, single gene disorders, or environmental causes can be responsible for microcephaly. Genetic diagnostic investigations can include fluorescence *in situ* hybridization (FISH) testing, karyotype, chromosomal microarray, and, most recently, whole-exome sequencing. Research is focusing on the role of genetic disease associated with (and perhaps causative of) abnormalities in the centrosomes, the organelles that serve as the main microtubule-organizing center of the cell. Centrosomal proteins control the mitotic spindle, which is essential for normal cell mitotic proliferation. Abnormalities of the centrosomes could be a central pathway in the development of microcephaly with abnormal neuronal production.

Gilmore EC, Walsh CA. Genetic causes of microcephaly and lessons for neuronal development. *Wiley Interdiscip Rev Dev Biol.* 2013;2(4):461–478.

9. Are older fathers at increased risk for having a child with a genetic disease?

Advanced paternal age is well documented as associated with **new dominant mutations**. The assumption is that the increased mutation rate is the result of the accumulation of new mutations from many cell divisions. The more cell divisions, the more likely an error (mutation) will occur. The mutation rate in fathers who are older than 50 years is five times higher than the mutation rate in fathers who are younger than 20 years. Autosomal dominant new mutations have been mapped and identified, including **achondroplasia, Apert syndrome**, and **Marfan syndrome**.

10. What is the most common genetic lethal disease?

Cystic fibrosis (CF). A genetic lethal disease is one that interferes with a person's ability to reproduce as a result of early death (before childbearing age) or impaired sexual function. CF is the most common autosomal recessive disorder in whites, occurring in 1 in 1600 infants (1 of every 20 individuals is a carrier for this condition) (Fig. 8.2). CF is characterized by widespread dysfunction of exocrine glands, chronic pulmonary disease, pancreatic insufficiency, and intestinal obstructions. Males are azoospermic. Survival rates have been increasing. Data from the Cystic Fibrosis Foundation Registry Report indicated that a baby born in the United States in 2016 with CF had a median predicted life expectancy of 47 years.

Cystic Fibrosis Foundation. www.cff.org. Accessed January 21, 2020.

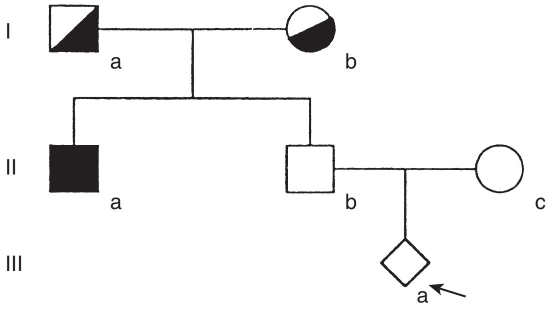

Fig. 8.2 Risk for cystic fibrosis (CF) in offspring of a mother with no family history of CF and a healthy father whose brother has CF. (1) Because IIa is affected with CF, both his parents must be carriers. (2) The chance of IIb being a carrier is 2 out of 3 because we know that he is not affected by CF. (3) The risk for IIc being a carrier is 1 in 20 (the population risk). (4) The chance of IIIa being affected is calculated as follows: father's carrier risk × mother's carrier risk × chance that both will pass on their recessive CF gene to their child = 2/3 × 1/20 × 1/4 = 1/120.

11. What syndromes are associated with macrosomia (large baby syndromes)?

- **Prader-Willi**: obesity, hypotonia, small hands and feet
- **Beckwith-Wiedemann**: macrosomia, omphalocele, macroglossia, ear creases
- **Sotos**: macrosomia, macrocephaly, large hands and feet
- **Weaver**: macrosomia, accelerated skeletal maturation, camptodactyly
- **Bardet-Biedl**: obesity, retinal pigmentation, postaxial polydactyly
- **Infants of diabetic mothers**

12. What is the "H_3O" of Prader-Willi syndrome?

Hyperphagia, hypotonia, hypopigmentation, and **obesity**. About 70% of Prader-Willi patients will have a deletion of an imprinted gene *SNPRN* on the long arm of paternally derived chromosome 15; in about 20% of these patients, both copies of the chromosome are maternally derived. The phenomenon in which a child inherits two complete or partial copies of the same chromosome from only one parent is referred to as *uniparental disomy*. The maternal uniparental disomy for chromosome 15 results in Prader-Willi syndrome, just as does a deletion of the paternal copy of the chromosome.

Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic and endocrine findings. *J Endocrinol Invest*. 2015;38(12):1249–1263.

Kalsner L, Chamberlin SJ. Prader-Willi, Angelman and 15q11-q13 duplication syndromes. *Pediatr Clin North Am*. 2015;62(3):587–606.

13. A child with supravalvular aortic stenosis, small and abnormally shaped primary teeth, low muscle tone with joint laxity, and elevated calcium noted on testing is likely to have what syndrome?

Williams syndrome, also known as *Williams-Beuren syndrome*. The genetic abnormalities result from microdeletions on chromosome 7 in an area that codes for the gene elastin. The loss of this gene is thought to contribute to the cardiac and musculoskeletal features found in Williams syndrome. Eighty percent of patients have cardiac abnormalities, most commonly arterial stenoses. Other characteristic features include frequent ear infections, hyperacusis (sensitivity to loud noises), failure to thrive at a younger age, and personality traits of a strong social orientation ("cocktail party personality") combined with anxiety problems.

Collins RT 2nd. Cardiovascular disease in Williams syndrome. *Curr Opin Pediatr.* 2018;30(5):609–615.

Prober BR. Williams-Beuren syndrome. *N Engl J Med.* 2010;362(3):239–252.

14. What are the two most common forms of dwarfism that are recognizable at birth?

- **Thanatophoric dwarfism:** This is the most common, but it is a *lethal* chondrodysplasia that is characterized by flattened, U-shaped vertebral bodies; telephone receiver–shaped femurs; macrocephaly; and redundant skinfolds that cause a puglike appearance. *Thanatophoric* means death loving (an apt description). The incidence is 1 in 20,000 births.
- **Achondroplasia:** This is the most common viable skeletal dysplasia, occurring in 1 in 26,000 live births. Its features are small stature, macrocephaly, depressed nasal bridge, lordosis, and a trident hand.

15. What chromosomal abnormality is found in cri-du-chat syndrome?

Cri-du-chat syndrome is the result of a deletion of material from the short arm of chromosome 5 (i.e., 5p-), which causes many problems, including growth restriction, microcephaly, and severe intellectual disability. Patients have a characteristic catlike cry during infancy, from which the syndrome derives its name. In 85% of cases, the deletion is a *de novo* event. In 15%, it is due to malsegregation from a balanced parental translocation.

16. Is there a "Catch-22" to the Catch-22 syndrome?

Unlike the Heller novel, this puzzle does have solutions, both genetic and acronymal. The acronym has been used to describe the salient features of **DiGeorge/velocardiofacial syndrome**:

- **C**ongenital heart disease (e.g., ventricular septal defect [VSD], truncus arteriosus, tetralogy of Fallot, aortic arch anomalies)
- **A**bnormal face (e.g., ear anomalies, wide-set eyes, long face, nasal abnormalities; Fig. 8.3)
- **T**hymic aplasia or hypoplasia
- **C**left palate
- **H**ypocalcemia (secondary to hypoparathyroidism)
- **22:** Microdeletion of chromosome 22q11

With so many names for the same condition, it is best to call the condition **chromosome 22q11.2 deletion syndrome**.

Sullivan KE. Chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. *Immuno Rev.* 2019;287(1):186–201.

McDonald-McGinn DM, Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Medicine (Baltimore).* 2011;90(1):1–18.

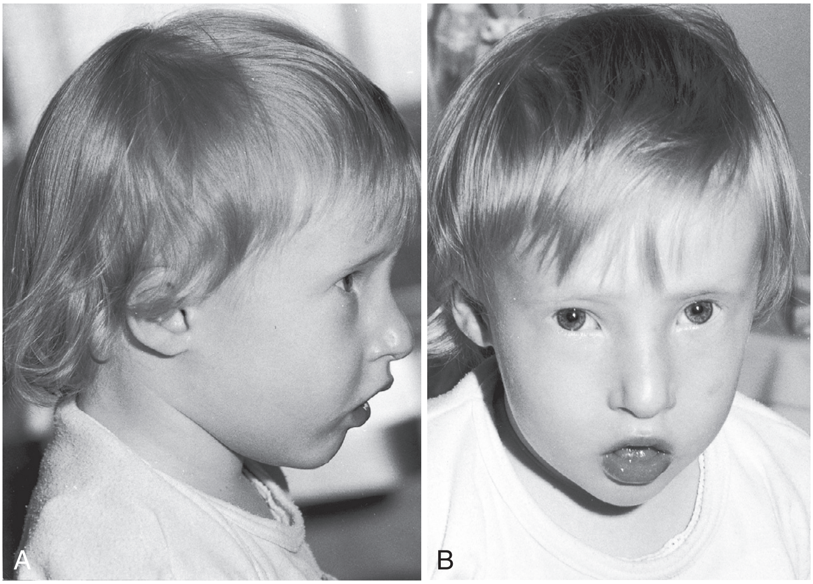

Fig. 8.3 Two-year-old with chromosome 22q11.2 deletion syndrome/DiGeorge syndrome. Facial dysmorphisms include hypertelorism, low-set ears, micrognathia, small fishlike mouth, short philtrum, malformed nose, and down-slanting palpebral fissures. The cardiac defect was truncus arteriosus. (From Perloff JK, Marelli AJ. *Perloff's Clinical Recognition of Congenital Heart Disease*. 6th ed. Philadelphia, PA: Saunders/Elsevier; 2012: 547.)

17. For what condition are patients with isolated limb hemihyperplasia (formerly called hemihypertrophy) at risk?

Embryonal cell tumors, including Wilms tumor, adrenal tumors, and hepatoblastoma. The risk in patients with isolated hemihyperplasia is about 6%; in patients with Beckwith-Wiedemann syndrome, it is 7.5%. Surveillance with α-fetoprotein measurements and abdominal ultrasounds every 3 months is recommended until the child is 4 years old and 8 years old, respectively. Alpha-fetoprotein measurements at 6-week intervals are preferred by some practitioners. In patients with Beckwith-Wiedemann syndrome, facial appearance is also distinctive (Fig. 8.4).

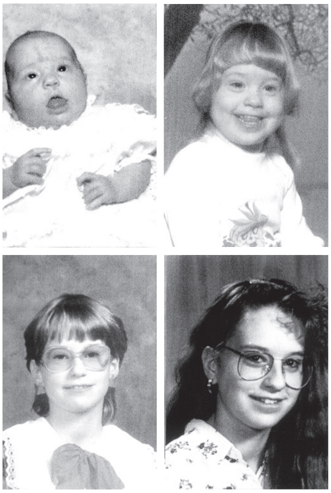

Fig. 8.4 Facial shape in Beckwith-Wiedemann syndrome, illustrated from birth to adolescence in a single person. In infancy and early childhood, the face is round with prominent cheeks and relative narrowing of the forehead. Note that by adolescence the trend is toward normalization. (From Allanson JE. Pitfalls of genetic diagnosis in the adolescent: the changing face. *Adolesc Med State Art Rev*. 2002;13:257–268.)

Of note, the term *hemihyperplasia* is more appropriate than the traditional term *hemihypertrophy*, because the pathologic growth process involves an abnormal proliferation of cells rather than an increase in the size of existing cells.

Kalish JM, Doros L, Helman LJ, et al. Surveillance recommendations for children with overgrowth syndromes and predispositions to Wilms tumor and hepatoblastoma. *Clin Cancer Res.* 2017;23(13):e115–e122.

18. After Down syndrome, what are the next most common autosomal trisomies in live-born children?

Trisomy 18 and **trisomy 13**. (See Table 8.2.)

Support Organization for Trisomy (SOFT) 18, 13 and Related Chromosome Disorders. www.trisomy.org. Accessed July 14, 2019.
Trisomy 18 Foundation. www.trisomy18.org. Accessed July 14, 2019.

Table 8.2 Differences Between Trisomy 18 and Trisomy 13

TRISOMY 18	TRISOMY 13
Edwards syndrome (described in 1960)	Patau syndrome (described in 1960)
≈1:8000 live births	≈1:20,000 live births
Clinical features: IUGR, elfin appearance failure to thrive, cardiac and kidney defects severe mental deficiency, micrognathia, microcephaly, posterior heel prominence prominent occiput, overlapping fingers	*Clinical features*: CNS malformations (holoprosencephaly), heart defects, genitourinary anomalies, growth retardation, polydactyly, cleft lip/palate, nasal malformation
Poor prognosis: 40% survive to 1 month; 5% survive to 1 year	*Poorer prognosis*: Only 50% survive >1 week; 5% to 6 months
80% female	Slight female predominance
Advanced maternal age: ↑↑risk	Advanced maternal age: ↑risk

CNS, Central nervous system; *IUGR,* intrauterine growth restriction.

19. What are the reasons that a condition might be genetically determined but the family history would be negative?

- Autosomal recessive inheritance
- X-linked recessive inheritance
- Spontaneous mutation
- Reduced penetrance (not all people with the genetic condition will show signs or symptoms of the genetic disorder)
- Variable expressivity (people with the same genetic condition can manifest different signs or symptoms)
- Incorrect paternity

20. What online resources are available for a pediatrician who suspects a child has a genetic syndrome or would like additional information about a patient already diagnosed with a genetic problem?

Two sites are particularly useful:

- **Online Mendelian Inheritance in Man** (OMIM; www.omim.org): This site is a comprehensive compendium of human genes and genetic phenotypes. It is now edited primarily under the auspices of Johns Hopkins University School of Medicine.
- **GeneReviews** (www.ncbi.nlm.nih.gov/books/NBK1116): This site provides a wealth of genetic information with disease descriptions, including diagnosis and management information. It is sponsored by the University of Washington at Seattle.

DOWN SYNDROME

21. What are the common physical characteristics of children with Down syndrome?

- Upslanted palpebral fissures with epicanthal folds
- Small, low-set ears with overfolded upper helices
- Short neck with excess skinfolds in newborns
- Prominent tongue
- Flattened occiput
- Exaggerated gap between first and second toe
- Hypotonia

(See Fig. 8.5.)

National Down Syndrome Society. www.ndss.org. Accessed January 18, 2020.

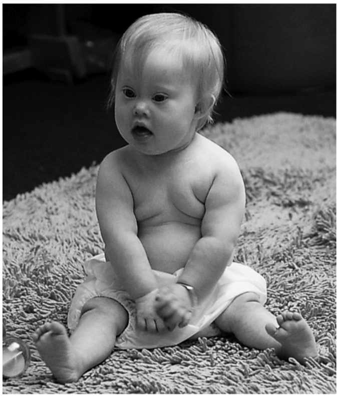

Fig. 8.5 Characteristic facies seen in Down syndrome. The child's posture is due to hypotonia. (From Lissauer T, Clayden G. *Illustrated Textbook of Paediatrics*. 4th ed. Philadelphia, PA: Elsevier; 2012:115-132.)

22. Are Brushfield spots pathognomonic for Down syndrome?

No. Brushfield spots are speckled areas that occur in the periphery of the iris (Fig. 8.6). They are seen in about 75% of patients with Down syndrome, but they also are found in up to 7% of newborns.

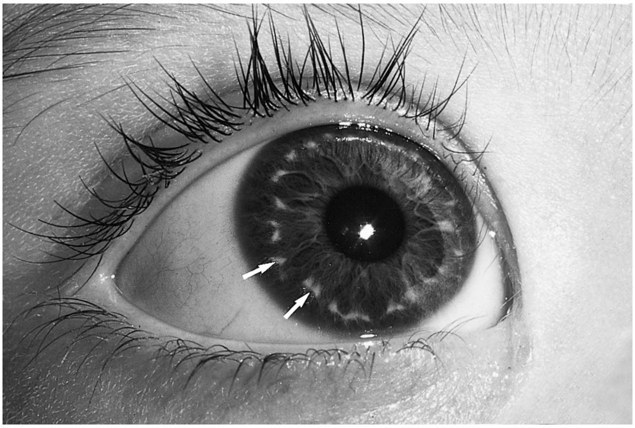

Fig. 8.6 Brushfield spots *(arrows)* consisting of depigmented foci along the circumference of the iris in a child with Down syndrome. (From Gatzoutis MA, Webb GD, Baubeney PEF, eds. *Diagnosis and Management of Adult Congenital Heart Disease*. 2nd ed. Philadelphia, PA: Saunders; 2011:29–47.)

23. What is the chance that a newborn with a simian crease has Down syndrome?

A single transverse palmar crease (Fig. 8.7) is present in 5% of newborns. Bilateral palmar creases are found in 1%. These features are twice as common in males as they are in females. However, about 45% of newborn infants with Down syndrome have a single transverse crease. Because Down syndrome occurs in 1 in 800 live births, the chance that a newborn with a simian crease has Down syndrome is only 1 in 60.

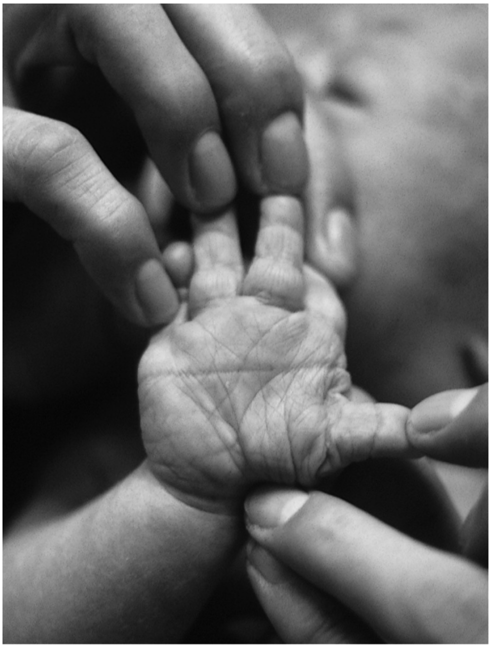

Fig. 8.7 Simian crease. (From Clark DA. *Atlas of Neonatology*. Philadelphia, PA: W.B. Saunders; 2000:31.)

24. Why is an extensive cardiac evaluation recommended for newborns with Down syndrome?

About 40% to 50% have congenital heart disease, but most infants are asymptomatic during the newborn period. Defects include atrioventricular canal (most common, 60%), VSD, and patent ductus arteriosus.

Bull, MJ; Committee on Genetics. Health supervision for children with Down syndrome. *Pediatrics*. 2011;128(2):393–406.

25. What proportion of infants with Down syndrome have congenital hypothyroidism?

About 2% (1 in 50), compared with 0.025% (1 in 4000) for all newborns, have congenital hypothyroidism. This emphasizes the importance of the state-mandated newborn thyroid screen. However, children with Down syndrome can become hypothyroid at any age.

Whooten R, Schmitt J, Schwartz A. Endocrine manifestations of Down syndrome. *Curr Opin Endocrinol Diabetes Obes*. 2018;25(1):61–66.

26. Infants with Down syndrome are at increased risk for a number of conditions during early infancy. What are they?

- **Gastrointestinal malformations**, including duodenal atresia and tracheoesophageal fistula
- **Hypothyroidism**
- **Lens opacities and cataracts**
- **Strabismus**
- **Hearing loss**, both sensorineural and conductive

Down Syndrome Research Foundation. www.dsrf.org. Accessed January 22, 2020.

KEY POINTS: INCREASED RISKS FOR PATIENTS WITH DOWN SYNDROME DURING THE NEWBORN PERIOD AND EARLY INFANCY

1. Congenital heart disease: atrioventricular canal defects, VSDs
2. Gastrointestinal malformations: duodenal atresia, tracheoesophageal atresia
3. Congenital hypothyroidism
4. Lens opacities and cataracts
5. Hearing loss

27. What is the most common malignancy in an infant with Down syndrome?

Leukemia. Its frequency in these individuals is 50-fold higher for younger children (0 to 4 years old) and 10-fold higher for individuals 5 to 29 years old, for a 20-fold increase in lifetime risk. Before leukemia becomes apparent, children with Down syndrome are at increased risk for other unusual white blood cell problems, including *transient myeloproliferative disorder* (a disorder of marked leukocytosis, blast cells, thrombocytopenia, and hepatosplenomegaly that spontaneously resolves) and a *leukemoid reaction* (markedly elevated white blood cell count with myeloblasts without splenomegaly, which also spontaneously resolves).

Seewald L, Taub JW, Maloney KW, et al. Acute leukemias in children with Down syndrome. *Mol Genet Metab.* 2012;107(1–2):25–30.

28. What is the genetic basis for Down syndrome?

The syndrome can be caused by trisomy of all or part of chromosome 21:

- Full trisomy 21: 94%
- Mosaic trisomy 21: 2.5%
- Translocation: 3.5%

29. What chromosomal abnormalities are related to maternal age?

All trisomies and **some sex chromosomal abnormalities** (except 45,X and 47,XYY) are related to maternal age.

30. How does the risk for having an infant with Down syndrome change with advancing maternal age?

See Table 8.3. Most cases of Down syndrome involve nondisjunction at meiosis I in the mother. This may be related to the lengthy stage of meiotic arrest between oocyte development in the fetus and the time of ovulation, which may occur up to 40 years later.

Table 8.3 Approximate Risk for Down Syndrome (Live Births) by Maternal Age

MATERNAL AGE (YR)	APPROXIMATE RISK FOR DOWN SYNDROME
All ages	1 in 650–800
20	1:1500
30	1:1000
35	1:385
40	1:110
45	1:37

From Lissauer T, Clayden G. *Illustrated Textbook of Paediatrics.* 4th ed. Philadelphia, PA: Elsevier; 2012:115–132.

31. Who was Down of Down syndrome?

John Langdon Down was a British physician. He originally described the condition that would later bear his name in 1866 based on measurements of the diameters of the head and palate and, in pioneering fashion, a series of clinical photographs taken in hospitals. His descriptions classified “mentally subnormal” patients on the basis of “ethnic classification” from which the widely used term “Mongolism” originated. It was not until 1961 that the term *Down’s syndrome* came into vogue at the urging of genetic experts. Eponymous diseases no longer carry the possessive form, and the condition is more properly referred to as *Down syndrome*.

Ward OC. John Langdon Down: the man and his message. *Downs Syndr Res Pract.* 1999;6(1):19–24.

DYSMORPHOLOGY

32. What is the clinical significance of a minor malformation?

The recognition of minor malformations in a newborn may serve as an indicator of altered morphogenesis or as a valuable clue to the diagnosis of a specific disorder. The presence of several minor malformations is unusual and often indicates a serious problem in morphogenesis. For example, when three or more minor malformations are discovered in a child, the risk for a major malformation also being present is >90%. The most common minor malformations involve the face, ears, hands, and feet. Almost any minor defect may occasionally be found as an unusual familial trait.

33. Do infants with the LEOPARD syndrome have spots?

This autosomal dominant condition, previously called LEOPARD syndrome, is now called *Noonan syndrome with multiple lentigines*. Yes, infants with this syndrome have multiple **l**entigines (darkly pigmented macules). See Fig. 8.8. Other features include:

- **L**entigines
- **E**lectrocardiogram abnormalities
- **O**cular hypertelorism
- **P**ulmonic stenosis
- **A**bnormal genitalia
- **R**etarded growth
- **D**eafness

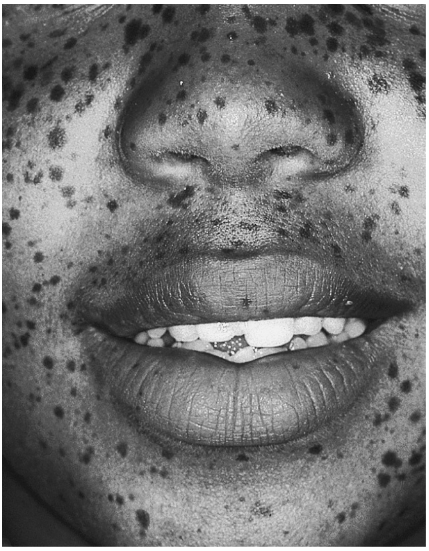

Fig. 8.8 Multiple lentigines in a 13-year-old with Noonan syndrome. (From Cohen BA. *Pediatric Dermatology*. 4th ed. Philadelphia, PA: Saunders Elsevier; 2013:151.)

34. Which is correct: CHARGE syndrome or CHARGE association?

CHARGE syndrome, formerly CHARGE association, is correct. A *syndrome* refers to a condition in which the underlying genetic cause has been identified. An *association* has signs and symptoms in combination greater than expected by chance alone but without a known genetic etiology. It is now known that CHARGE syndrome is an autosomal dominant condition, and almost all cases are due to *de novo* mutations in the *CHD7* gene. Rare familial cases have been reported. *CHD7* (chromodomain helicase DNA-binding protein 7) is the only gene currently known to be affected in CHARGE syndrome. In 70% of CHARGE syndrome patients, a mutation can be identified in this gene.

Hsu P, Ma A, Wilson M, et al. CHARGE syndrome: a review. *J Paediatr Child Health*. 2014;50(7):504–511.

35. What is the proper way to test for low-set ears?

The designation is made when the upper portion of the ear (helix) meets the head at a level below a horizontal line drawn from the inner canthi of palpebral fissure. The best way to measure is to align a straight edge between the inner canthi and extend the line toward the ear to determine whether the ears lie completely below this plane (Fig. 8.9). In normal individuals, about 10% of the ear is above this plane.

Hunter A, Frias J, Gillessen-Kaesbach G, et al. Elements of morphology: standard terminology for the ear. *Am J Med Genet A*. 2009;149A(10):40–60.

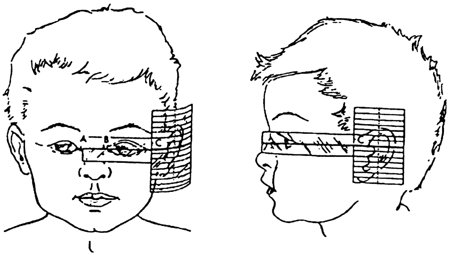

Fig. 8.9 How to test for low-set ears. (From Feingold M, Bossert WH. Normal values for selected physical parameters: an aid to syndrome delineation. In Bergsma D, ed. *The National Foundation—March of Dimes Birth Defects Series*. 1974;10:9.)

36. What is the significance of preauricular pits?

Preauricular pits go by various names, including preauricular sinuses and preauricular cysts. These are the indentations or holes found anywhere along the ear, but most commonly anterior to the helix and superior to the tragus of the ear (Fig. 8.10). They are very common, occurring in up to 1% of white, 5% of black, and 10% of Asian infants, and may occur bilaterally in 25% to 50%. In 3% to 10% of cases, they may be associated with other conditions (deafness) or syndromes (e.g., branchio-oto-renal [BOR] syndrome). Repeated infections can occur, which can require surgical excision.

Roth DA, Hildesheimer M, Bardenstein S, et al. Preauricular skin tags and ear pits are associated with permanent hearing impairment in newborns. *Pediatrics.* 2008;122(4):e884–e890.

Scheinfeld NS, Silverberg NB, Weinberg JM, Nozad V. The preauricular sinus: a review of its clinical presentation, treatment and associations. *Pediatr Dermatol.* 2004;21(3):191–196.

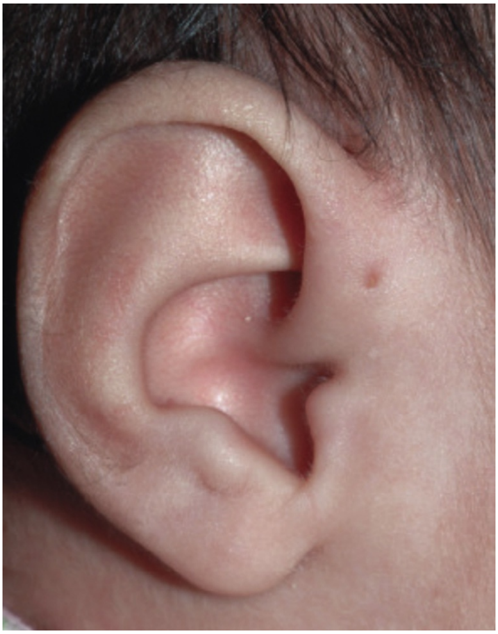

Fig. 8.10 Preauricular pit. (From Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Philadelphia, PA: Elsevier; 2018:1923.).

37. How is hypertelorism distinguished from telecanthus?

Hypertelorism is wide spacing of the eyes in which the interpupillary distance is increased. Hypertelorism can be a normal variant or may be seen in cranial abnormalities, such as Noonan syndrome, and multiple other syndromes. *Telecanthus* occurs when the inner canthi are laterally displaced but the interpupillary distance is normal. Telecanthus can be seen in fetal alcohol syndrome and Waardenburg syndrome (Fig. 8.11). The eyes appear widely spaced but are not. *Hypotelorism* (not shown in figure) is a shortening of the interpupillary distance. Standard distances are found in various reference sources.

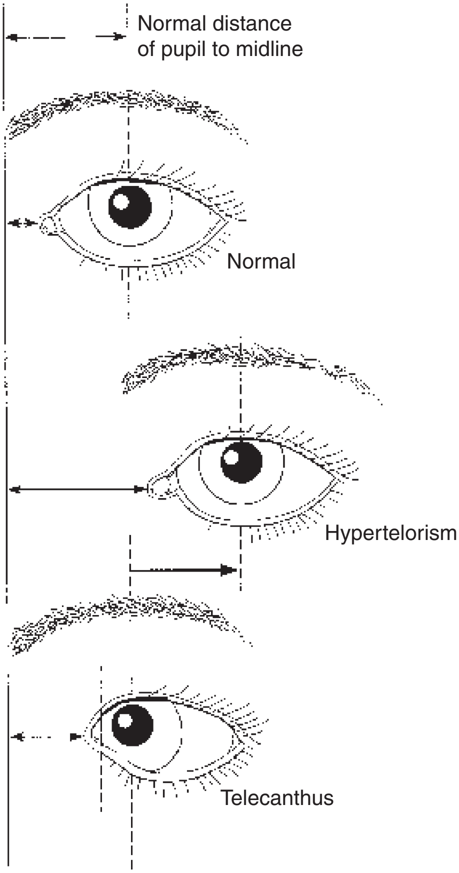

Fig. 8.11 Normal versus hypertelorism versus telecanthus. (From Goldbloom RB. *Pediatric Clinical Skills*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011:63.)

38. What is the inheritance pattern of cleft lip and palate?

Most cases of cleft lip and palate are inherited in a polygenic or multifactorial pattern. The male-to-female ratio is 3:2, and the incidence in the general population is about 1 in 1000. Recurrence risk after one affected child is 3% to 4%; after two affected children, it is 8% to 9%.

Leslie EJ, Marazita ML. Genetics of cleft lip and cleft palate. *Am J Med Genet C Semin Med Genet*. 2013;163C(4):246–258.

39. Which syndromes are associated with colobomas of the iris?

Colobomas (defects) of the iris (Fig. 8.12) are the result of abnormal ocular development and embryogenesis. They are frequently associated with chromosomal syndromes (most commonly trisomy 13, 4p-, 13q-) and cat-eye syndrome. In addition, they may be commonly found in patients with the CHARGE syndrome, Goltz syndrome, and Rieger syndrome. Whenever iris colobomas are noted, chromosome analysis is recommended. The special case of complete absence of the iris (aniridia) is associated with the development of Wilms tumor and may be caused by a deletion or point mutation of the *PAX6 gene* on chromosome 11p.

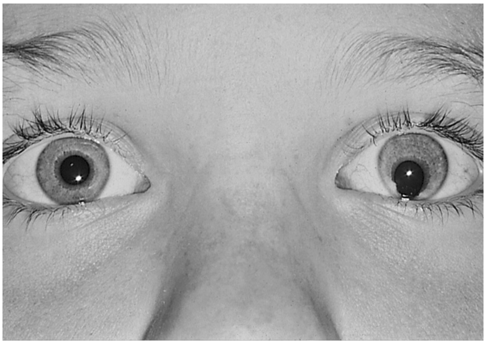

Fig. 8.12 Left iris coloboma. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis*. 4th ed. St. Louis, MO: Mosby; 2002:674.)

GENETIC PRINCIPLES

40. What are the common symbols used in the construction of a pedigree chart?

See Fig. 8.13.

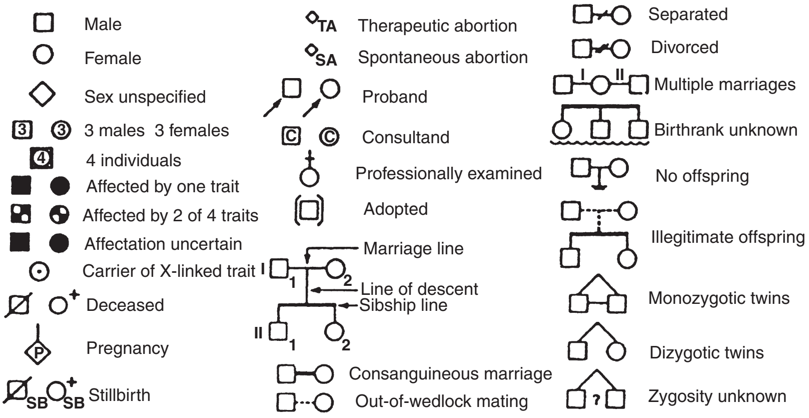
Male
Female
Sex unspecified
3 3
3 males 3 females
4
4 individuals
Affected by one trait
Affected by 2 of 4 traits
Affectation uncertain
Carrier of X-linked trait
Deceased
P
Pregnancy
SB SB
Stillbirth
TA
Therapeutic abortion
SA
Spontaneous abortion
Proband
C C
Consultand
Professionally examined
Adopted
Marriage line
I
1
2
Line of descent
Sibship line
II
1
2
Consanguineous marriage
Out-of-wedlock mating
Separated
Divorced
I
II
Multiple marriages
Birthrank unknown
No offspring
Illegitimate offspring
Monozygotic twins
Dizygotic twins
?
Zygosity unknown

Fig. 8.13 Symbols used in the construction of a pedigree chart.

41. How can the same genotype lead to different phenotypes?

In *parental imprinting* (an area of the regulation of gene expression that is incompletely understood), the expression of an identical gene is dependent on whether the gene is inherited from the mother or the father. For example, in patients with Huntington disease, the clinical manifestations occur much earlier if the gene is inherited from the father rather than the mother. Modification of the genes by methylation of the DNA during development has been hypothesized as one explanation of the variability.

42. When a geneticist says they are going "FISH"-ing, what does that mean?

FISH is a molecular cytogenetic technique that is used to identify abnormalities of chromosome number or structure using a single-stranded DNA probe (for a known piece of DNA or chromosome segment). The probe is labeled with a fluorescent tag and targeted to a single-strand DNA that has been denatured in place on a microscope slide. The use of fluorescent microscopy enables the detection of more than one probe, each of which is labeled with a different color. FISH is commonly used for the rapid prenatal diagnosis of trisomies with the use of amniotic fluid or chorionic villi using interphase cells from cultured specimens and probes for the most common chromosomal abnormalities (13, 18, 21, X, and Y). Although interphase FISH for prenatal diagnosis has low false-positive and false-negative rates, it is considered investigational and is used only in conjunction with standard cytogenetic analysis.

43. What is currently the best method for detecting small chromosome deletions and duplications?

Single nucleotide polymorphism array (SNP array) is currently the best method of detecting DNA copy number variations (CNVs). This test scans the whole genome for variations in DNA copy numbers. Standard chromosome analysis can detect chromosomal imbalances that are at least 5 Mb in size, whereas SNP array is able to detect cryptic changes (deletions and duplications) that are not visible on standard chromosome analysis. It has become the method of choice for infants and children with multiple congenital anomalies and/or developmental delays. Five percent of such children have visible abnormalities on routine chromosome analysis, but an additional 10% to 15% will have an abnormality when screened with SNP array. It has come to replace FISH analysis for detection of conditions such as chromosome 22q11.2 deletion syndrome and Williams syndrome. It is important to note that not all CNVs are deleterious; some are polymorphisms that are frequently carried by one parent. Parental studies are thus important in interpreting the comparative genomic hybridization, a molecular cytogenetic method for analyzing the CNV results, when the results are not clear.

Schaaf CP, Wiszniewska J, Beaudet AL. Copy number and SNP arrays in clinical diagnosis. *Annu Rev Genomics Hum Genet.* 2011; 12:25–51.

Shaffer LG, Bejjani BA. Using microarray-based molecular cytogenic methods to identify chromosome abnormalities. *Pediatr Ann.* 2009;38(8):440–447.

INBORN ERRORS OF METABOLISM

44. What types of inherited metabolic conditions are routinely screened by most states?

Organic acidemias, amino acid disorders, fatty acid oxidation defects, homocystinuria, galactosemia, and biotinidase deficiency. Some states screen for Krabbe, Pompe, and X-linked adrenoleukodystrophy as well.

Villoria JG, Pajares S, López RM, et al. Neonatal screening for inherited metabolic diseases in 2016. *Semin Pediatr Neurol.* 2016; 23(4):257–272.

45. In what settings should inborn errors of metabolism (IEM) be suspected?

- Onset of symptoms correlating with dietary changes
- Loss or leveling of developmental milestones
- Patient with strong food preferences or aversions
- Parental consanguinity
- Unexplained sibling death, mental retardation, or seizures
- Unexplained failure to thrive
- Unusual odor
- Hair abnormalities, especially alopecia
- Microcephaly or macrocephaly
- Abnormalities of muscle tone
- Organomegaly
- Coarsened facial features, thick skin, limited joint mobility, hirsutism
- Cardiomyopathy
- Liver disease
- Rhabdomyolysis and muscle weakness
- Recurrent vomiting
- Seizures and encephalopathy

46. What are the main categories of specialized laboratory testing to detect an IEM?

- Plasma amino acids
- Plasma acylcarnitines
- Urine organic acids
- Carnitine analysis (blood and urine)
- Enzymatic assays for specific disorders
- Molecular testing for specific disorders (single gene testing, panels, or whole-exome sequencing)

47. What are the main principles of treatment for IEM?

- Removal of the offending compound
- Use of special diets and supplements (medical foods) to provide appropriate nutrition, to keep offending compounds at minimum, and to avoid deficiencies
- Use of medication that helps eliminate toxic compounds (e.g., ammonia scavengers) or to block the production of toxic compounds (e.g., nitisone in tyrosinemia type I)
- Use of enzyme replacement therapies available for specific conditions (e.g., lysosome storage disorders)
- Bone marrow/hematopoietic stem cell transplant for selected disorders
- Gene therapy

Gambello MJ, Li H. Current strategies for the treatment of inborn errors of metabolism. *J Genet Genomics.* 2018;45(2):61–70.

Saudubray JM, Berghe G, Walter JH, eds. *Inborn Metabolic Diseases: Diagnosis and Treatment.* 5th ed. Berlin and Heidelberg, Germany: Springer Verlag; 2012:103–109.

48. What is gene therapy?

Gene therapy is a type of targeted therapy by which there is transfer via a vector (e.g., various viruses) of normal human genetic material into target cells for the correction of altered, mutated, or missing genes. The field is in its infancy with applications largely in experimental research, but there is the potential to treat diseases caused by recessive gene disorders (such as CF and sickle cell disease) and acquired genetic disorders (e.g., certain cancers).

Heimall J. Genetic testing to diagnose primary immunodeficiency disorders and to identify targeted therapy. *Immunol Allergy Clin North Am.* 2019;39(1):129–140.

Goncalves GAR, Paiva RMA. Gene therapy: advances, challenges and perspectives. *Einstein (Sao Paulo).* 2017;15(3):369–375.

49. What are the main features of phenylketonuria (PKU)?

PKU is a defect in the hepatic enzyme phenylalanine hydroxylase, which results in an inability to metabolize one amino acid (phenylalanine) to another (tyrosine). Phenylalanine accumulates with toxic consequences. Untreated infants will develop developmental delay, intellectual disability, and later seizures. Clinical clues include musty-smelling infant sweat (due to phenylacetate, a phenylalanine breakdown product) and light-colored skin and hair due to tyrosine deficits, a component of melanin. PKU is the most frequent IEM, with an incidence of about 1:12,000. Inheritance is autosomal recessive. Carriers are asymptomatic. Treatment involves dietary manipulation to limit phenylalanine exposure, supplementation with other amino acids, and pharmacotherapy to reduce serum phenylalanine levels boosting enzyme activity (cofactor use). Early identification, as through newborn screening, and early treatment result in an excellent prognosis, but treatment is for life.

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van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis.* 2017;12;12(1):162.

Greene CL, Longo N. National Institutes of Health (NIH) review of evidence in phenylalanine hydroxylase deficiency (phenylketonuria) and recommendations/guidelines from the American College of Medical Genetics (ACMG) and Genetics Metabolic Dietitians International (GMDI). *Mol Genet Metab.* 2014;112:85–86.

50. What are the main characteristics of a patient with glycogen storage disease type 1 (GSD 1)?

GSDs, of which there are 11 types, involve defects in glycogen synthesis or breakdown in multiple organs, including muscles and liver. Type I (von Gierke disease), the most common, and others are listed in Table 8.4.

- The cardinal feature of von Gierke disease is fasting hypoglycemia.
- The main defect is in the enzyme glucose-6-phosphatase that allows glucose to be released from the liver into the bloodstream while removing phosphate from glucose (as long as glucose is phosphorylated, it cannot pass through the hepatocyte cell membrane).
- Additional laboratory markers are lactic acidemia, increased uric acid, and increased triglycerides.
- Clinical features include growth retardation, short stature, hepatomegaly, prominent abdomen, developmental delay/intellectual disability (if not treated), and acute symptoms associated with hypoglycemia (i.e., tremors, sweating, tachycardia, lethargy, seizures, coma, etc.).
- Treatment is based on adequate supply of glucose: continuous feedings, frequent meals, uncooked cornstarch, and overnight feedings.
- Outcome is good with proper treatment.

Ellingwood SS, Cheng A. Biochemical and clinical aspects of glycogen storage diseases. *J Endocrinol.* 2018;238(3):R131–R141.

Vanier MT. Lysosomal diseases: biochemical pathways and investigations. *Handb Clin Neurol.* 2013;113:1695–1699.

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Table 8.4 Most Common Glycogen Storage Disorders

TYPE ENZYME DEFICIENCY	MAIN FEATURES	LABORATORY	TREATMENT
I: Type Ia (Von Gierke) glucose-6-phosphatase	Truncal obesity, hepatomegaly, "doll face," nephromegaly, short stature, failure to thrive	Hypoglycemia after short fasting (3-4 hours), acidosis, elevated lactate, uric acid, and triglycerides	Avoidance of fasting using frequent meals, overnight continuous feeds, and uncooked cornstarch
I: Type Ib Glucose-6-phosphate transporter	Same as type Ia + neutropenia, leukocyte dysfunction, bacterial infections, diarrhea, inflammatory bowel disease (IBD)	Same as type Ia + neutropenia and leukocyte dysfunction	Same as type Ia + granulocyte colony growth factor
II (Pompe) α-glucosidase (acid maltase)	*Infantile:* cardiomyopathy, hypotonia, failure to thrive. *Juvenile/adult:* progressive muscle weakness	No hypoglycemia	Enzyme replacement therapy (ERT): aglucosidase. High-protein diet
III (Cori) debranching enzyme	Type IIIa: same as type Ia, but less hypoglycemia, normal kidneys, myopathy, cardiomyopathy Type IIIb: only liver	Hypoglycemia, normal lactate and uric acid	Avoidance of fasting using frequent meals, overnight continuous feeds, and uncooked cornstarch
IV (Andersen) Branching enzyme	*Classic:* failure to thrive, hepatomegaly, progressive liver disease (liver failure, cirrhosis). *Neuromuscular form:* myopathy and cardiomyopathy	No hypoglycemia	Liver transplant
VI (Hers) Liver phosphorylase	Hepatomegaly, mild hypoglycemia, often asymptomatic	Mild hypoglycemia, elevated lactate and liver enzymes	Avoidance of fasting using frequent meals and uncooked cornstarch
IX Phosphorylase kinase (X-linked)	Hepatomegaly, mild hypoglycemia, often asymptomatic	Mild hypoglycemia, elevated lactate and liver enzymes	Avoidance of fasting using frequent meals and uncooked cornstarch

51. What are the main features of a patient with mucopolysaccharidosis (MPS)?

Mucopolysaccharidoses are examples of storage diseases of lysosomes, which are intracellular organelles where degradation of macromolecules takes place. When individual enzymes are deficient, metabolites accumulate predominantly in the tissues that are primarily responsible for their degradation (e.g., heparin sulfate in the CNS, dermatan sulfate in bone and liver). All disorders are autosomal recessive except for type II (Hunter syndrome), which is X-linked recessive. Patients are usually normal at birth, although sometimes they might have symptoms already. Subsequent clinical features include progressive facial and skin changes (due to accumulation of storage material in the connective tissue compartment), progressive skeletal deformities including growth restriction, bone dysplasia and contractures, and hepatomegaly. Depending on the type, there may be progressive psychomotor retardation with loss of acquired skills and intellectual disability, if the storage material affects the CNS. Treatment, when available, may involve enzyme replacement therapy and hematopoietic stem cell transplantation. Diagnosis is based on analysis of glycosaminoglycans (mucopolysaccharides) in urine, x-rays, enzymatic analysis, and molecular testing. See Table 8.5.

Ferreira CR, Gahl WA. Lysosomal storage diseases. *Transl Sci Rare Dis.* 2017;25;2(1-2):1–71.
Vanier MT. Lysosomal diseases: biochemical pathways and investigations. *Handb Clin Neurol.* 2013;113:1695–1699.

52. An 8-month-old presents with vomiting, lethargy, hypoglycemia, and no ketones on urinalysis. What condition is likely?

Medium-chain acyl-CoA dehydrogenase deficiency (MCAD). Disorders of fatty-acid oxidation or a deficiency of carnitine (the principal transporter of fatty acids into mitochondria) can result in maladaptation to the fasting stress that often accompanies an intercurrent illness. Hypoketotic or nonketotic hypoglycemia results from the inability to utilize fatty acids, which are the primary source of ketones. Screening for this condition is done in newborn screening programs. The clinical presentation varies, including no symptoms, but a presentation can be dramatic with severe vomiting, encephalopathy, coma, and death.

53. What features should raise suspicion of mitochondrial disease?

Most mitochondrial diseases are *progressive* and *multisystemic*. Suspicion about a mitochondrial disorder should be raised if (1) the patient has either muscle disease and involvement of two additional organ systems (one of which may be the CNS), or (2) involvement of the CNS plus two other systems, or (3) multisystem disease (at least three systems) including muscle and/or the CNS. Organ systems affected are those with high energy demand, such as skeletal and cardiac muscle, endocrine organs, kidney, retina, and CNS. Any infant with unexplained failure to thrive, weakness, hypotonia, and a metabolic acidosis (particularly lactic acidosis) should be evaluated for a possible mitochondrial disorder.

Gorman GS, Chinnery PF, DiMauro S, et al. Mitochondrial diseases. *Nat Rev Dis Primers.* 2016;2:16080.
Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics.* 2007;120(6):1326–1333.

54. What is the most common presentation of childhood-onset mitochondrial disease?

Leigh syndrome. This is a progressive neurodegenerative condition that involves developmental regression, pyramidal signs, and brainstem dysfunction (e.g., dystonia, strabismus, nystagmus, swallowing problems), hypotonia, and lactic acidosis. It is also known as *subacute necrotizing encephalomyelopathy.* Etiology can be due to mutation in the mitochondrial DNA (mtDNA), autosomal recessive mutations (*SURF1*; a nuclear gene), or X-linked (*PDHA1*) mutations. The prognosis is poor.

Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics.* 2007;120(6):1326–1333.

55. When you are rounding in the well-newborn nursery, one of the infants has an unusual odor. What body and urine odors are typically associated with inherited metabolic disorders?

- **Musty, mildewy**: PKU
- **Maple syrup**: maple syrup urine disease (MSUD)
- **Sweaty feet**: isovaleric aciduria (IVA), glutaric aciduria type II
- **Cat urine**: 3-methylcrotonylglycinuria, multiple carboxylase deficiency
- **Cabbage**: tyrosinemia type 1

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Table 8.5 Most Common Mucopolysaccharidoses

TYPE ENZYME DEFICIENCY	CLINICAL FEATURES	DIAGNOSIS	MANAGEMENT
Type I (Hurler: severe) α-L-Idurodinase	Onset first year of life; coarse facial features, corneal clouding, failure to thrive, recurrent upper respiratory infections, developmental delay, cardiac disease, hepatosplenomegaly	Increased dermatan and heparan sulfate in urine. Enzymatic assay. Molecular testing (*IDUA* gene)	Enzyme replacement (ERT) for non-CNS features. BMT/HSCT below $2^{1}/_{2}$ years to treat *all* features, including CNS.
Type I (Sheie: milder) α-L-Idurodinase	Onset in adolescence and adulthood; normal intelligence, mostly normal height, mild skeletal deformities, degenerative joint disease, corneal clouding, cardiac valve disease	Increased dermatan and heparan sulfate in urine. Enzymatic assay. Molecular testing (*IDUA* gene)	Symptomatic; ERT
Type II (Hunter) Iduronate-2-sulfatase	Joint contractures, obstructive and restrictive airway disease, cardiac disease, skeletal deformities, cognitive decline. Mild form (adult onset).	X-linked. Normal corneas. Increased dermatan and heparan sulfates. Enzymatic assay. Molecular testing (*IDS* gene).	ERT for non-SNC features. Possible BMT or HSCT.
Type III (Sanfilippo) Four enzymes of the heparan sulfate metabolism	Encephalopathy with mild organ involvement; development/language delay, behavioral problems, sleep deprivation, hyperactivity, intellectual disability, seizures, neurodegeneration.	Increased heparan sulphate in urine. Enzymatic assay. Molecular testing (four different genes).	Symptomatic.
Type IV (Morquio) Two enzymes of keratan sulfate metabolism	Normal intelligence. Short stature. Skeletal deformities, short neck, scoliosis, joint contractures, atlanta-axial instability.	Increased keratan sulfate in urine. Abnormal skeletal x-rays. Enzyme assays. Molecular testing for two genes.	Symptomatic. ERT.
Type VI (Maroteaux-Lamy disease) arylsulfatase-B	Normal intelligence, skeletal deformities similar to Type I (Hurler). Often macrocephaly at birth.	Increased dermatan sulfate in urine. Enzymatic assay. Molecular testing (*ARSB* gene).	ERT.

BMT, Bone marrow transplant; *HSCT,* hematopoietic stem cell transplant.

- **Rancid butter**: tyrosinemia type 1
- **Sulfur**: cystinuria, tyrosinemia type 1
- **Fishlike**: trimethylaminuria, dimethylglycinuria

56. Which IEMs can result in fetal hydrops?

- **Lysosomal disorders**: MPS type VII, sialidosis, mucolipidosis type II (I-cell disease), sphingolipidosis (Niemann-Pick type A, Gaucher, Farber, GM1 gangliosidosis, etc.), lipid storage disorders (Niemann-Pick type C), sialic storage disorders
- **Sterol synthesis disorders**: Smith-Lemli-Opitz syndrome, mevalonic aciduria
- **Peroxisomal disorders**: Zellweger
- **Glycogen storage disease** type IV (Anderson disease)
- **Glycosylation disorders**
- **Primary carnitine deficiency**
- **Mitochondrial disorders**
- **Neonatal hemochromatosis**

57. Which metabolic disorders can present as sudden unexplained death in infancy (SUDI)?

- Fatty-acid oxidation defects
- Some organic acidemias
- Defects of aldosterone and glucocorticoid metabolism
- McArdle syndrome (myophosphorylase deficiency)
- Mitochondrial defects (e.g., Leigh syndrome)

Takahashi T, Yamada K, Kobayashi H, et al. Metabolic disease in 10 patients with sudden unexplained death in infancy or acute life threatening events. *Pediatr Int*. 2015;57(3):348–353.

58. One of the infants in your care dies from a suspected IEM. What postmortem investigations are key to elucidate the diagnosis?

- **Serum and plasma:** Centrifuge several milliliters immediately, freeze in separate fractions.
- **Dried blood spot***:* Obtain on filter paper card.
- **Urine:** Freeze immediately; consider bladder wash with saline.
- **Bile:** Obtain spot on filter card for acylcarnitine analysis.
- **DNA:** Obtain 3 to 10 mL whole blood in EDTA tube; if necessary freeze without centrifuging.
- **Culture fibroblasts:** Skin biopsy, may be obtained up to 24 hours postmortem.
- **Cerebrospinal fluid (CSF):** Obtain several 1-mL fractions; freeze immediately, if possible at −70°C.
- **Muscle biopsy:** DNA, histology, histochemistry, enzymatic studies (energy metabolism)
- **Liver biopsy:** histochemistry, enzymatic assays

SEX CHROMOSOME ABNORMALITIES

59. Does the Lyon hypothesis refer to the "king of beasts"?

The *Lyon hypothesis* states that, in any cell, only one X chromosome will be functional. Any other X chromosomes present in that cell will be condensed, late replicating, and inactive (called the *Barr body*). The inactive X chromosome may be either paternal or maternal in origin, but all descendants of a particular cell will have the same inactive parentally derived chromosome.

60. What are the features of the four most common sex chromosome abnormalities?

See Table 8.6.

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Table 8.6 Most Common Sex Chromosome Disorders

	47,XXY (KLINEFELTER)	**47,XYY**	**47,XXX**	**45,X (TURNER)**
Frequency of live births (males)	1 in 1000	1 in 1000	—	—
Frequency of live births (females)	—	—	1 in 1000	1 in 2000–2500
Maternal age association	+	—	+	—
Phenotype	Tall, eunuchoid habitus, underdeveloped secondary sexual characteristics, gynecomastia (XXY)	Tall, severe acne, indistinguishable from normal males (XYY)	Tall, indistinguishable from normal females (XXX)	Short stature, webbed neck, shield chest, pedal edema at birth, coarctation of the aorta (45,X)
IQ and behavior problems	80-100; behavioral problems (XXY)	90-110; behavioral problems; aggressive behavior (XYY)	90-110; behavioral problems (XXX)	Mildly deficient to normal intelligence; spatial-perceptual difficulties (45,X)
Reproductive function	Extremely rare (XXY)	Common (XYY)	Common (XXX)	Extremely rare (45,X)
Gonad	Hypoplastic testes; Leydig cell hyperplasia, Sertoli cell hypoplasia, seminiferous tubule dysgenesis, few spermatogenic precursors (XXY)	Normal-size testes, normal testicular histology (XYY)	Normal-size ovaries, normal ovarian histology (XXX)	Streak ovaries with deficient follicles (45,X)

From Donnenfeld AE, Dunn LK. Common chromosome disorders detected prenatally. *Postgrad Obstet Gynecol.* 1986;6:5.

61. Of the four most common types of sex chromosome abnormalities, which is identifiable at birth?

Only infants with **Turner syndrome** have physical features that are easily identifiable at birth (see Fig. 8.14).

Milbrandt T, Thomas E. Turner syndrome. *Pediatr Rev.* 2013;34(9):420–421.

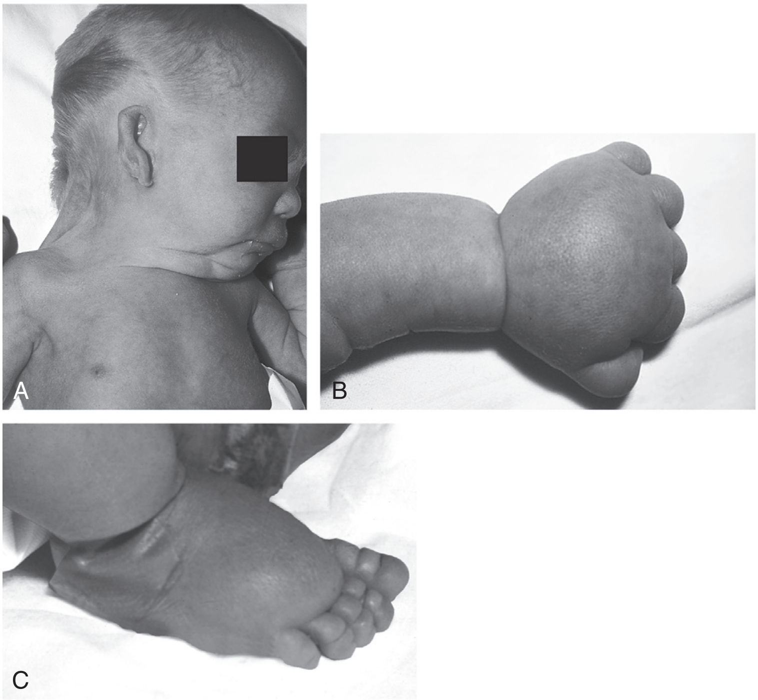

Fig. 8.14 Newborn with Turner syndrome with (A) short, webbed neck with low posterior hairline, shield chest with wide-spaced nipples, micrognathia, and (B and C) lymphedema of hands and feet, including toes. Lymphedema of the toes can lead to nail hypoplasia. (From Zitelli BJ, McIntire SC, Nowalk AJ, eds. *Atlas of Pediatric Physical Diagnosis.* 6th ed. Philadelphia, PA: Saunders; 2012:15.)

KEY POINTS: TURNER SYNDROME

1. Majority: 45,X
2. Newborn period: Only sign may be lymphedema of feet and/or hands
3. Adolescence: Primary amenorrhea due to ovarian dysplasia
4. Short stature often prompts initial workup
5. Normal mental development
6. Classic features: Webbed neck with low hairline, broad chest with wide-spaced nipples
7. Increased risk for congenital heart disease: Coarctation of the aorta

62. What are the differences between Noonan syndrome and Turner syndrome?

See Table 8.7.

Table 8.7 Differences Between Turner Syndrome and Noonan Syndrome

TURNER SYNDROME	NOONAN SYNDROME
Affects females only	Affects both males and females
Chromosome disorder	Normal chromosomes
(45,X)	Autosomal dominant disorder
Near-normal intelligence	Mental deficiency
Coarctation of aorta is the most common	Pulmonary stenosis is the most common
Amenorrhea and sterility due to ovarian dysgenesis	Normal menstrual cycle in females

63. What is the second most common genetic form of intellectual disability?

Fragile X syndrome (with Down syndrome being the most common). The prevalence is estimated to be 1 in 3600 to 4000 in males and 1 in 4000 to 6000 in females. About 2% to 6% of male subjects and 2% to 4% of female subjects with unexplained intellectual disability will carry the full fragile X mutation.

FRAXA Research Foundation. www.fraxa.org. Accessed January 23, 2020.
National Fragile X Foundation. www.fragilex.org. Accessed January 23, 2020.

64. What are the characteristic facial features of fragile X syndrome?

Typical features include a long face, long everted ears, prominent mandible, and large forehead. These tend to be more evident in affected adults. In younger children, the prominent features are prominent ears (Fig. 8.15).

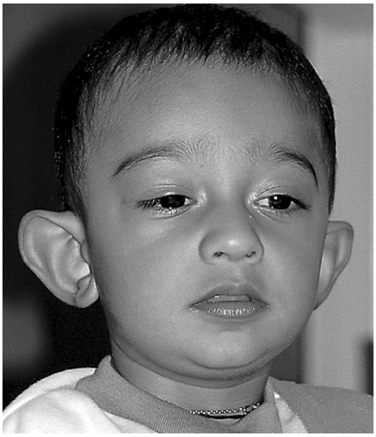

Fig. 8.15 A child with fragile X. At this age, the main feature is often the prominent ears. (From Lissauer T, Clayden G. *Illustrated Textbook of Paediatrics*. 4th ed. Philadelphia, PA: Elsevier; 2012:115–132.)

65. What is the nature of the mutation in fragile X syndrome?

Expansion of trinucleotide repeat sequences. When the lymphocytes of an affected male are grown in a folate-deficient medium and the chromosomes examined, a substantial fraction of X chromosomes demonstrate a break near the distal end of the long arm. This site—the fragile X mental retardation-1 gene (*FMR1*)—was identified and sequenced in 1991. At the center of the gene is a repeating trinucleotide sequence (CGG) that, in normal individuals, repeats 6 to 45 times. However, in carriers, the sequence expands to 50 to 200 copies (called a *premutation*). In fully affected individuals, it expands to 200 to 600 copies.

Bagni C, Oostra BA. Fragile X syndrome: from protein function to therapy. *Am J Med Genet A.* 2013;161A:2809–2821.

66. What are the associated medical problems of fragile X syndrome in males?

Flat feet (80%), macro-orchidism (80% after puberty), mitral valve prolapse (50% to 80% in adulthood), recurrent otitis media (60%), strabismus (30%), refractive errors (20%), seizures (15%), and scoliosis (>20%).

Lachiewicz AM, Dawson DV, Spiridigliozzi GA. Physical characteristics of young boys with fragile X syndrome: reasons for difficulties in making a diagnosis in young males. *Am J Med Genet.* 2000;92(4):229–236.

67. What is the outcome for girls with fragile X?

Heterozygous females who carry the fragile X chromosome have more behavioral and developmental problems (including attention-deficit/hyperactivity disorder), cognitive difficulties (50% with an IQ in the intellectual disability or borderline range), and physical differences (prominent ears, long and narrow face). Cytogenetic testing is recommended for all sisters of fragile X males.

Visootsak J, Hipp H, Clark H, et al. Climbing the branches of a family tree: diagnosis of fragile X syndrome. *J Pediatr.* 2014; 164(6):1292–1295.

KEY POINTS: FRAGILE X SYNDROME

1. Second most common cause of inherited intellectual disability
2. Prepubertal: Elongated face, flattened nasal bridge, protruding ears
3. Pubertal: Macro-orchidism
4. Heterozygous females: 50% with IQ in the borderline or intellectually disabled range
5. First recognized trinucleotide repeat disorder

TERATOLOGY

68. Which drugs are known to be teratogenic?

Most teratogenic drugs exert a deleterious effect in a minority of exposed fetuses. Exact malformation rates are unavailable because of the inability to perform a statistical evaluation on a randomized, controlled population. Known teratogens are summarized in Table 8.8.

Table 8.8 Known Teratogens

DRUG	MAJOR TERATOGENIC EFFECT
Thalidomide	Limb defects
Lithium	Ebstein tricuspid valve anomaly
Aminopterin	Craniofacial and limb anomalies
Methotrexate	Craniofacial and limb anomalies
Phenytoin	Facial dysmorphism, dysplastic nails
Trimethadione	Craniofacial dysmorphism, growth retardation
Valproic acid	Neural tube defects
Diethylstilbestrol	Müllerian anomalies, clear cell adenocarcinoma
Androgens	Virilization
Tetracycline	Teeth and bone maldevelopment
Streptomycin	Ototoxicity
Warfarin	Nasal hypoplasia, bone maldevelopment
Penicillamine	Cutis laxa
Accutane (retinoic acid)	Craniofacial and cardiac anomalies

69. What are the characteristic features of fetal hydantoin syndrome?

- **Craniofacial:** Broad nasal bridge, wide fontanel, low-set hairline, broad alveolar ridge, metopic ridging, short neck, ocular hypertelorism, microcephaly, cleft lip and palate, abnormal or low-set ears, epicanthal folds, ptosis of eyelids, coloboma, and coarse scalp hair
- **Limbs:** Small or absent nails, hypoplasia of distal phalanges, altered palmar crease, digital thumb, and dislocated hip

  About 10% of infants whose mothers took phenytoin (Dilantin) during pregnancy have a major malformation; 30% have minor abnormalities.

Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformation and prenatal outcomes. *BMC Med.* 2017;5;15(1):95.

70. How much alcohol is safe to drink during pregnancy?

This is **unknown**. The full dysmorphologic manifestations of fetal alcohol syndrome are associated with heavy intake. However, most infants will not display the full syndrome. For infants born to women with lesser degrees of alcohol intake during pregnancy and who demonstrate more subtle abnormalities (e.g., cognitive and behavioral problems), it is more difficult to ascribe risk because of confounding variables (e.g., maternal illness, pregnancy weight gain, other drug use [especially marijuana]). Furthermore, for reasons that are unclear, it appears that infants who are prenatally exposed to similar amounts of alcohol are likely to have different consequences. Because current data (including a 2014 meta-analysis) do not support the concept that any amount of alcohol is safe during pregnancy, the American Academy of Pediatrics recommends abstinence from alcohol for women who are pregnant or who are planning to become pregnant.

Williams JF, Smith VC. Fetal alcohol spectrum disorders. *Pediatrics.* 2015;136(5):e1395–1406.

Sowell SR, Charness ME, Riley EP. Pregnancy: no safe level of alcohol. *Nature.* 2014;513(7517):172.

Flak AL, Su S, Bertrand J, et al. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. *Alcohol Clin Exp Res.* 2014;38(1):214–226.

71. What are the frequent facial features of fetal alcohol syndrome?

The three facial dysmorphisms found most characteristically are **short palpebral fissures**, **thin vermillion border**, and **smooth philtrum**. Additional features include:

- **Skull:** Microcephaly, midface hypoplasia
- **Eyes:** Epicanthal folds, ptosis, strabismus
- **Mouth:** Prominent lateral palatine ridges, retrognathia in infancy, micrognathia or relative prognathia in adolescence
- **Nose:** Flat nasal bridge, short and upturned nose (Fig. 8.16)

Wozniak JR, Riley EP, Charness ME. Clinical presentation, diagnosis and management of fetal alcohol spectrum disorder. *Lancet.* 2019; 18(8):760–770.

Williams JF, Smith VC. Fetal alcohol spectrum disorders. *Pediatrics.* 2015;136(5):e1395–e1406.

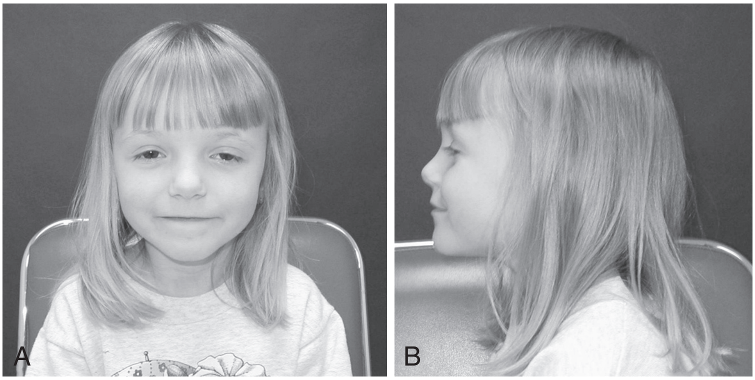

Fig. 8.16 Patient with fetal alcohol syndrome. (A) Note bilateral ptosis, short palpebral fissures, smooth philtrum, and thin upper lip. (B) Short palpebral fissures are sometimes more noticeable in profile. Head circumference is second percentile. (From Seaver LH. Adverse environmental exposures in pregnancy: teratology in adolescent medicine practice. *Adolesc Med State Art Rev*. 2002;13:269–291.)

KEY POINTS: FETAL ALCOHOL SYNDROME

1. Growth deficiencies: Prenatal and postnatal
2. Microcephaly with neurodevelopmental abnormalities
3. Short palpebral fissures
4. Smooth philtrum
5. Thin upper lip

72. What happens to children with fetal alcohol syndrome when they grow up?

Follow-up studies of adolescents and adults revealed that relatively short stature, poorly developed philtrum, thin upper lip, and microcephaly persisted, but other facial anomalies became more subtle. Persistent mental handicaps (including intellectual disabilities), problematic academic functioning (particularly in mathematics), limited occupational options, and dependent living were major sequelae. Intermediate or significant maladaptive behavior was also a very common finding. Severely unstable family environments were common.

Spohr HL, Willms J, Steinhausen HC. Fetal alcohol spectrum disorders in young adulthood. *J Pediatr.* 2007;150(2):175–179.
Streissguth AP, Aase JM, Clarren SK, et al. Fetal alcohol syndrome in adolescents and adults. *JAMA.* 1991;265(15):1961–1967.
National Organization on Fetal Alcohol Syndrome. www.nofas.org. Accessed January 10, 2020.

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CHAPTER 9

HEMATOLOGY

Jennifer L. Webb, MD, MSCE and Steven E. McKenzie, MD, PhD

BONE MARROW FAILURE

1. What are the types of bone marrow failure?

Bone marrow failure is manifested by pancytopenia or, at times, by cytopenia of a single cell type. It can be **acquired** (acquired aplastic anemia) or **inherited/genetic** (e.g., Fanconi anemia, severe congenital neutropenia, Diamond-Blackfan anemia, amegakaryocytic thrombocytopenia, thrombocytopenia-absent radius, dyskeratosis congenita).

Sieff CA. Introduction to acquired and inherited bone marrow failure. *Hematol Oncol Clin North Am.* 2018;32(4):569–590.
Chirnomas SD, Kupfer GM. The inherited bone marrow failure syndromes. *Pediatr Clin North Am.* 2013;60(6):1291–1310.

2. What are the causes of acquired aplastic anemia?

After careful exclusion of the known causes listed here, 80% of cases remain classified as **idiopathic**. A variety of associated conditions include the following:

- **Radiation**
- **Immune diseases:** eosinophilic fasciitis; hypogammaglobulinemia
- **Drugs and chemicals**
  - *Regular*: Cytotoxic (as in treatment for malignancy), benzene
  - *Idiosyncratic*: Chloramphenicol, anti-inflammatory drugs, antiepileptics, gold, nifedipine
- **Viruses**: Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis (primarily B), parvovirus (in immunocompromised hosts), HIV
- **Thymoma**
- **Pregnancy**
- **Paroxysmal nocturnal hemoglobinuria**
- **Preleukemia**

Shimamura A, Guinana EC. Acquired aplastic anemia. In Nathan DG, Orkin SD, Ginsburg D, Look AT, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 6th ed. Philadelphia, PA: W.B. Saunders; 2003:257.

3. What is the definition of severe aplastic anemia?

Severe disease includes a **hypocellular bone marrow biopsy** ($<30\%$ of the normal hematopoietic cell density for age) and **decreases in at least two out of three peripheral blood counts**: neutrophil count <500 cells/mm^3, platelet count $<20{,}000$ cells/mm^3, or reticulocyte count $<1\%$ after correction for the hematocrit. Categorization has important prognostic and therapeutic implications.

4. What are the treatments and prognosis for children with aplastic anemia?

In the absence of definitive treatment, $<20\%$ of children with severe acquired aplastic anemia survive for >2 years. When bone marrow transplantation is performed using a human leukocyte antigen (HLA)–identical sibling donor, the 2-year survival rate exceeds 90%. The usual approach to the newly diagnosed child with severe acquired aplastic anemia is to perform bone marrow transplantation if there is an HLA-identical sibling to serve as the donor. About 80% of children with severe aplastic anemia do not have a sibling donor for bone marrow transplantation. These children receive medical therapy, usually the combination of antithymocyte globulin, cyclosporine, and hematopoietic growth factors, such as granulocyte colony-stimulating factor (GCSF). Two-year response rates are 30% to 70%, and survival rates exceed 90% in children. Matched unrelated bone marrow transplants have historically only been considered in patients who fail medical therapy; however, they may be considered earlier in patients with severe aplastic anemia who have features that indicate a potential poor response to medical therapy.

Yoshida N, Kojima S. Updated guidelines for the treatment of acquired aplastic anemia in children. *Curr Oncol Rep.* 2018;20(9):67.
Scheinberg P, Wu CO, Nunez O, et al. Long-term outcome of pediatric patients with severe aplastic anemia treated with antithymocyte globulin and cyclosporine. *J Pediatr.* 2008;153(6):814.

5. What is the probable diagnosis of a 6-year-old child with pancytopenia, short stature, abnormal thumbs, and areas of hyperpigmentation?

Fanconi anemia, or constitutional aplastic anemia, is a genetic disorder in which numerous physical abnormalities are often present at birth, and aplastic anemia occurs around the age of 5 years. The more common physical abnormalities include hyperpigmentation, anomalies of the thumb and radius, small size, microcephaly, and renal anomalies (e.g., absent, duplicated, or pelvic horseshoe kidneys). Patients with Fanconi anemia are also susceptible to leukemia and epithelial carcinomas.

6. How is the diagnosis of Fanconi anemia made?

Chromosomal breakage analysis, for example, with diepoxybutane or mitomycin C, can be used to make the diagnosis, and **molecular diagnosis** can confirm the diagnosis and be used to test relatives. In studies of peripheral blood lymphocytes, a high percentage of patients with Fanconi anemia will have chromosomal breaks, gaps, or rearrangements. Many genes causing the Fanconi anemia syndrome are critical for DNA repair, explaining patients' predisposition to cancers and sensitivity to chemotherapy. Molecular diagnosis has assumed increasing importance, as studies linking genotype and phenotype can be predictive.

Triemsta J, Pham A, Rhodes L, et al. A review of Fanconi anemia for the practicing pediatrician. *Pediatr Ann.* 2015;44(10):444–445, 448, 450.

De Rocco D, Bottega R, Cappelli E, et al. Molecular analysis of Fanconi anemia: the experience of the Bone Marrow Failure Study Group of the Italian Association of Pediatric Onco-Hematology. *Haematology.* 2014;99(6):1022–1031.

Walden H, Deans AJ. The Fanconi anemia DNA repair pathway: structural and functional insights into a complex disorder. *Annu Rev Biophys.* 2014;43:257–278.

7. A 1-year-old child presents with pallor and lethargy and is found to have a normocytic anemia (hemoglobin 3.5 g/dL). The white blood cell (WBC) and platelet count are normal, and the examination is otherwise unremarkable. The reticulocyte count is 0.2%. What are two possible causes of this clinical scenario?

Transient erythroblastopenia of childhood (TEC) and **Diamond-Blackfan anemia**. Both are disorders of red blood cell (RBC) production that occur during early childhood. Both disorders are characterized by a low hemoglobin level and an inappropriately low reticulocyte count. The bone marrows of patients with these conditions may be indistinguishable, showing reduced or absent erythroid activity in both cases.

8. Why is distinguishing between the two conditions extremely important?

TEC is a **self-limited disorder**, whereas *Diamond-Blackfan* syndrome usually **requires lifelong treatment**.

9. How are the two conditions diagnosed?

- **Age of presentation**: Although there is an overlap in the age of presentation, Diamond-Blackfan syndrome commonly causes anemia during the first 6 months of life, whereas TEC occurs more frequently after the age of 1 year.
- **Red cells:** The red cells in patients with Diamond-Blackfan syndrome have fetal characteristics that are useful for distinguishing this disorder from TEC, including increased mean cell volume, elevated level of hemoglobin F, and presence of i antigen.
- **Adenosine deaminase:** The level of adenosine deaminase may be elevated in patients with Diamond-Blackfan syndrome but normal in children with TEC.
- **Mutations:** Twenty-five percent of white patients with Diamond-Blackfan anemia have been found to have mutations in the gene for ribosomal protein S19, and molecular diagnosis for these mutations is very helpful when positive. Recently additional gene mutations have been identified in Diamond-Blackfan anemia. These also affect ribosomal proteins. In total, about three-fourths of Diamond-Blackfan patients can be identified by mutational analysis.

Bartels M, Bierings M. How I manage children with Diamond–Blackfan anemia. *Br J Haematol.* 2019;184(2):123–133.

Viachos A, Ball S, Dahl N, et al. Diagnosing and treating Diamond Blackfan anemia: results of an international clinical conference. *Br J Hematol.* 2008;142(6):859–876.

10. What is Kostmann syndrome?

Kostmann syndrome is severe congenital neutropenia. At birth, or shortly thereafter, very severe neutropenia (absolute neutrophil count of 0 to 200/mm^3) is noted, often at the time of significant bacterial infection (e.g., deep skin abscess, pneumonia, sepsis). Even with antibiotic treatment, there is a high mortality during infancy unless GCSF therapy is used to elevate the neutrophil count. Some recipients of GCSF have survived the infection risk but have developed myelodysplastic syndrome or acute myeloid leukemia. Therefore individualized judgment and monitoring are essential in GCSF treatment of severe congenital neutropenia. An alternative treatment is bone marrow transplantation from an HLA-identical sibling donor. Patients with Kostmann syndrome may have mutations in *ELANE* or *HAX1* genes.

Donadieu J, Beaupain B, Fenneteau O, Bellanné-Chantelot C. Congenital neutropenia in the era of genomics: classification, diagnosis and natural history. *Br J Hematol.* 2017;179(4):557–574.

11. A 4-year-old with failure to thrive and chronic diarrhea has a normal sweat test but is noted to have neutropenia on a routine complete blood count (CBC). What is the most likely diagnosis?

Shwachman-Diamond syndrome is characterized by exocrine pancreatic dysfunction (causing steatorrhea), skeletal abnormalities (e.g., metaphyseal dysostosis, which are defects in normal cartilage ossification), growth retardation, and bone marrow insufficiency leading to neutropenia. It may initially be misdiagnosed as cystic fibrosis (CF) because of overlapping symptoms, but can be distinguished because sweat chloride levels are normal and mutations in the CF gene are lacking. Genetic testing for mutations in the *SBDS* (Schwachman-Bodian-Diamond syndrome) gene is diagnostic.

Nelson AS, Myers KC. Diagnosis, treatment and molecular pathology of Shwachman-Diamond syndrome. *Hematol Oncol Clin North Am.* 2018;32(4):687–700.

Burroughs L, Woolfrey A, Shimamura A. Shwachman-Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am.* 2009;23(2):233–248.

COAGULATION DISORDERS

12. What features on history or physical examination help pinpoint the cause of a bleeding problem?

- **Platelet problems**: Although there can be considerable overlap, in general, platelet problems result in petechiae, especially on dependent parts of the body and mucosal surfaces. Additional manifestations of platelet disorders include epistaxis, hematuria, menorrhagia, and gastrointestinal (GI) hemorrhages.
- **Coagulation factor deficiencies or platelet problems**: Ecchymoses are suspicious for coagulation factor deficiencies or platelet problems when they occur in unusual areas, are out of proportion with the extent of described trauma (also seen in child abuse), or are present in different stages of healing. Delayed bleeding from old wounds and extensive hemorrhage (particularly into joint spaces or after immunizations) are also suggestive of coagulation protein disorders.
- **Disseminated intravascular coagulation (DIC)**: Bleeding from multiple sites in an ill patient is worrisome for DIC. If a patient has tolerated tonsillectomy and/or adenoidectomy or extraction of multiple wisdom teeth without major hemorrhage, a significant inherited bleeding disorder is unlikely.

Rodriguez V, Warad D. Pediatric coagulation disorders. *Pediatr Rev.* 2016;37(7):279–291.

13. What do the activated partial thromboplastin time (aPTT) and the prothrombin time (PT) measure in the basic clotting cascade?

See Fig. 9.1.

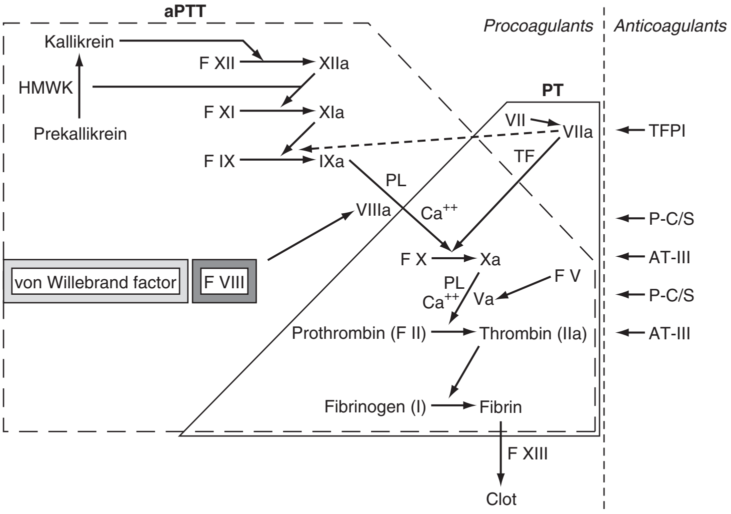

Fig. 9.1 Simplified pathways of blood coagulation. The area inside the dotted line is the intrinsic pathway measured by the activated partial thromboplastin time (aPTT). The area inside the solid line is the extrinsic pathway, measured by the prothrombin time (PT). The area encompassed by both lines is the common pathway. *AT-III,* Antithrombin III; *F,* factor; *HMWK,* high-molecular-weight kininogen; *P-C/S,* protein C/S; *PL,* phospholipid; *TFPI,* tissue factor pathway inhibitor. (From Marcdante KJ, Kliegman RM: Hemostatic disorders. In Marcdante KJ, Kliegman RM, eds. *Nelson Essentials of Pediatrics*, 8th ed. Philadelphia, PA: Elsevier, 2019, 581.)

14. What are the possible causes of a prolonged aPTT and PT?

See Table 9.1.

Table 9.1 Common Causes of Prolonged Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT)

SCENARIO	COMMON AND IMPORTANT CAUSES	COMMENTS
Prolonged PT	Vitamin K deficiency Liver disease Warfarin Factor VII deficiency Disseminated intravascular coagulation (DIC)	Isolated PT elevation is a sensitive marker early in DIC development
Prolonged aPTT	Von Willebrand disease Hemophilia (factor VIII, IX, or XI deficiency)	Rare deficiencies of factor XII, congenital abnormalities of the receptor for vitamin B_{12}–intrinsic factor complex
	Heparin	Gastric mucosal defects that interfere with the secretion of intrinsic factor or phosphokinase may also elevate aPTT but are not clinically significant
	Antiphospholipid antibodies (associated with minor infections or, rarely, autoimmune or thromboembolic disease)	Half of children with prolonged aPTT do not have a bleeding disorder
Prolonged PT and aPTT	Heparin Warfarin Liver disease DIC	Fibrinogen measurement can help distinguish among liver disease and DIC (decrease in fibrinogen) and vitamin K (no decrease in fibrinogen)

From Savage W, Takemoto C. Bleeding and bruising. *Contemp Pediatr.* 2009;26:66.

15. What is the international normalized ratio (INR)?

The *INR*, introduced in an attempt to standardize the PT, results from a calculation in which an individual patient's PT test value is divided by the laboratory's pooled normal plasma standard PT, then raised to an exponent applicable to each individual PT-initiating reagent available. Its utility is in monitoring Coumadin (warfarin) use, in that the reported value has clinical utility, regardless of which laboratory performed the PT test. The INR for individuals with normal coagulation proteins not receiving Coumadin therapy is 1.0 (± ≈0.1 to 0.2 based on that laboratory's upper and lower range). For those receiving Coumadin therapy, the desired INR varies with the condition being treated, but it is often 2.0 to 3.0.

16. What is thromboelastography (TEG)?

TEG is a whole-blood test of coagulation. Blood is rotated gently, and the timing to clot initiation (**R**eaction time), speed of clot formation (**K**inetic time), thrombin burst (α angle, which is the slope of the line between R and K, a measurement of the rate of clot formation), clot strength (**Maximal A**mplitude, or **MA**), and clot lysis time are measured. These measurements can assess platelet function, clot strength, and fibrinolysis in a way that other testing cannot. It is used often in surgery or in trauma settings to direct blood product use.

Carter BG, Carland E, Monagle P, et al. Impact of thromboelastography in paediatric intensive care. *Anaesth Intensive Care.* 2017; 45(5):589–599.

17. What are the frequency and inheritance patterns of common bleeding disorders?

- **von Willebrand disease:** This is the most common coagulopathy, and it is autosomal dominant in the majority of cases. Frequency is estimated to be between 1 in 100 and 1 in 500.
- **Factor VIII deficiency** (hemophilia A) and **factor IX deficiency** (hemophilia B): These conditions are inherited in an X-linked pattern so that females are carriers and males are affected. Inquiry about affected maternal male first cousins or uncles is appropriate. In general, heterozygotes for clotting factor deficiencies are not clinically affected. Factor VIII deficiency is more common (1 in 5000) than factor IX deficiency, affecting 80% to 85% of all patients with clinically diagnosed factor deficiency.

Rodriguez V, Warad D. Pediatric coagulation disorders. *Pediatr Rev.* 2016;37(7):279–291.

18. Why is the lack of a family history of bleeding problems only moderate evidence against the likelihood of hemophilia A in a patient?

The abnormal factor VIII gene responsible for hemophilia A exhibits marked heterogeneity, and **up to one-third of cases** (either the immediate-carrier mother or the son himself) **may have developed a spontaneous mutation**.

Molecular diagnosis of the most common mutation in severe factor VIII deficiency—a gene inversion in the distal portion of the gene in the affected male, the mother, and maternal relatives—may help the physician with understanding the family history.

19. What are the clinical classifications for hemophilia A and B?

- **Severe:** <1% factor VIII or IX activity; spontaneous bleeding common; bleeding often involves joints, soft tissue, brain (intracranial hemorrhages in neonates), postcircumcision; most common type (50% to 70% of cases)
- **Moderate:** 1% to 5% factor VIII or IX activity; bleeding after minor trauma, but not usually spontaneous; may involve joints and soft tissue, but less commonly central nervous system (CNS) or postcircumcision; least common type (10% of cases)
- **Mild:** 6% to 30% factor VIII or IX activity; bleeding only after major trauma or surgery; joint and soft tissue involvement, but uncommon after circumcision; more common than moderate type (30% to 40% of cases)

Sharathkumar AA, Pipe SW. Bleeding disorders. *Pediatr Rev.* 2008;29(4):121–129.
National Hemophilia Foundation. www.hemophilia.org. Accessed January 10, 2020.

20. What are the primary measures for achieving hemostasis in individuals with bleeding disorders?

Never forget anatomic or surgical technical causes and corrections for hemorrhage. As a result, primary measures are local measures (“push on it, put a stitch or staple in it”), supplemented occasionally with licensed topical prothrombotic agents. Replacement of the deficient blood component(s) is also important, but pharmacologic measures such as desmopressin acetate (DDAVP, which increases von Willebrand factor), antifibrinolytics such as epsilon aminocaproic acid and tranexamic acid (which stabilize clots), and topical hemostatic preparations can be useful.

21. To what degree should factor levels be raised for patients with hemophilia with or without life-threatening hemorrhage?

The following guidelines are applicable to patients with moderate (1% to 5% of normal factor levels) to severe (<1% of normal) hemophilia:

- For *minor hemorrhages* (e.g., small muscle or oral), factor levels should be increased to 20% to 30% of normal.
- For *major bleeding episodes* (e.g., hip bleeds, intracranial hemorrhage, bleeding around the airway), factor levels should be raised 70% to 100%, and repeat dosing should be strongly considered under close medical supervision.

22. How are doses of replacement factors calculated?

Recombinant factor VIII and factor IX concentrates are the treatments of choice. Each unit of factor VIII or factor IX is equivalent to the activity of 1 mL of normal plasma. With the recombinant products, a dose of 1 unit/kg should increase the factor VIII level by 1.5% to 2% and the factor IX level by 1%. Calculations can be made as follows:

$$\text{Factor VIII dose (units)} = (\text{Goal \% Increase}) \times (\text{kg}) \times 0.5$$

$$\text{Factor IX dose (units)} = (\text{Goal \% Increase}) \times (\text{kg})$$

For example: If you have a 28-kg patient with a head bleed and severe factor VIII deficiency that you wish to correct 100%, your goal dose is 100 × 28 × 0.5 = 1400 units.

Another example: If you have a 50-kg patient with a minor bleed and severe factor IX deficiency that you wish to correct 30%, your goal dose is 30 × 50 = 1500 units.

Always round up to the nearest vial size so that there is no wastage of recombinant factor.

Of note, if there is an antibody inhibitor of the replacement factor, correction will not be achieved. Under these circumstances, alternative therapies are needed, such as porcine factor VIII, factor VIII inhibitor bypassing activity complexes, or recombinant factor VIIa.

Josephson N. The hemophilias and their clinical management. *Hematology Am Soc Hematol Educ Program.* 2013;2013:261–267.

23. In patients with severe hemophilia, can prophylaxis with factor replacement prevent severe hemorrhage?

In a study of boys with severe hemophilia A who were given regular recombinant factor VIII infusions up to 6 years of age, prophylaxis prevented joint damage and decreased the frequency of joint and other hemorrhages. Prophylaxis works. However, the cost is between $200,000 and $300,000 annually. Emicizumab, a recombinant humanized monoclonal antibody, has been approved by the Food and Drug Administration (FDA) since 2017 for prophylaxis in patients with hemophilia A without inhibitors and since 2018 for patients with inhibitors. Other therapies involving recombinant bioengineering are in development. How to reconcile the benefits and costs of effective expensive therapies remains a challenge for the health care system.

Weyand AC, Pipe SW. New therapies for hemophilia. *Blood.* 2019;133(5):389–398.

Acharya SS. Advances in hemophilia and the role of current and emerging prophylaxis. *Am J Manag Care.* 2016;22(5 Suppl):s116–s125.
Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med.* 2007;357(6):535–544.

24. What are the half-lives of exogenously administered factors VIII and IX?

The half-lives for the *first* doses of factors VIII and IX are 6 to 8 hours and 4 to 6 hours, respectively. With *subsequent* doses, factor VIII has a half-life of 8 to 12 hours, whereas factor IX has a half-life of 18 to 24 hours. Thus, for serious bleeding, the second dose of factor VIII should be given 6 to 8 hours after the first, whereas the second dose of factor IX should be given 4 to 6 hours after the first. Subsequent doses are usually given every 12 hours for factor VIII replacement and every 24 hours for factor IX replacement, but the measurement of actual factor levels may be necessary to guide therapy in life-threatening situations.

Gill JC. Transfusion principles for congenital coagulation disorders. In Hoffman R, Benz EJ, Shattil SJ, et al, eds. *Hematology: Basic Principles and Practice*. 3rd ed. New York: Churchill Livingstone; 2000:2282.

25. Are longer-acting factors VIII and IX available?

Both long-acting recombinant factor IX and long-acting recombinant factor VIII are approved in the United States. They significantly affect the frequency of dosing for factor, especially because each is used for prophylaxis. The half-lives are extended by fusion with the Fc moiety of immunoglobulin G (IgG), which prevents lysosomal degradation of the factor. Other mechanisms to prevent degradation and prolong the half-life of factors VIII and IX, including PEGylation (the process of covalent attachment of polyethylene glycol [PEG] polymer chains to the recombinant factors) and albumin fusion, are also available. Gene therapy also holds future promise for long-term cure.

Shapiro A. Long-lasting recombinant factor VIII proteins for hemophilia A. *Hematology Am Soc Hematol Edu Program.* 2013;2013:37–43.

26. What can cause an elevation of the PT when other coagulation testing is normal?

Factor VII deficiency. PT measures the function of the common pathway factors (including X, V, II, and fibrinogen) and the extrinsic pathway (tissue factor and factor VII). The aPTT measures the common pathway plus the function of the intrinsic pathway (including factors XII, XI, IX, and VIII). Isolated factor VII deficiency selectively elevates the PT. Other causes of elevated PT (e.g., liver disease, vitamin K deficiency, Coumadin toxicity) are not selective for lowering factor VII activity.

27. Who gets hemophilia C?

More commonly called *factor XI deficiency,* this is an uncommon type of hemophilia ($<$5% of total hemophilia patients). Unlike the X-linked nature of hemophilias A and B, it is an autosomal recessive disease that occurs most frequently in Ashkenazi Jews. Plasma levels of factor XI are less predictive of clinical bleeding.

Asakai R, Chung DW, Davie EW, et al. Factor XI deficiency in Ashkenazi Jews in Israel. *N Engl J Med.* 1991;325(3):153–158.

28. Why is factor IX deficiency (hemophilia B) also commonly called "Christmas disease"?

In 1952, investigators in England noted that when blood from one group of hemophiliacs was added to the blood of another group of hemophiliacs, the clotting time was shortened. This provided the basis for the discovery of plasma substances in addition to what was then called "antihemophilic globulin" (and now called factor VIII), which is responsible for normal clotting. The name was derived because the first patient examined in detail with the unusual clotting deficiency (later designated as factor IX) was a boy named Stephen Christmas. The publication of the landmark article in fact occurred during the last week of December in 1952.

Biggs R, Douglas AS, Macfarlane RG, et al. Christmas disease: a condition previously mistaken for haemophilia. *Br Med J.* 1952; 2(4799):1378–1382.

KEY POINTS: HEMOPHILIA

1. X-linked recessive disorder
2. Hemophilia A: Factor VIII abnormalities (80% to 85% of total cases)
3. Hemophilia B: Factor IX abnormalities
4. Severity based on factor levels: Severe ($<$1%), moderate (1% to 5%), mild (5% to 30%)
5. Common initial presentation: Bleeding after circumcision

29. What is the von Willebrand factor (vWF)?

Synthesized in megakaryocytes and endothelial cells, vWF is a large multimeric protein that binds to collagen at points of endothelial injury. It serves as a bridge between damaged endothelium and adhering platelets, and it facilitates platelet attachment. It also serves as a carrier protein for factor VIII in circulation; it minimizes the clearance of factor VIII from plasma and accelerates its cellular synthesis.

30. What are the coagulation abnormalities in von Willebrand disease?

von Willebrand disease is actually a group of disorders caused by qualitative or quantitative abnormalities in vWF. Coagulation abnormalities in children with severe disease can include a prolonged bleeding time, prolonged PTT, decreased factor VIII coagulant activity, decreased factor VIII antigen, and decreased ability of patient plasma to induce aggregation of normal platelets in the presence of ristocetin (the so-called "ristocetin cofactor activity").

Sharma R, Flood VH. Advances in diagnosis and treatment of Von Willebrand disease. *Blood.* 2017;130(22):2386–2391.

31. What are the initial diagnostic tests for suspected von Willebrand disease?

- Quantification of vWF antigen
- Measurement of vWF function (either ristocetin-based platelet aggregation test, known as *ristocetin cofactor assay*) or vWF collagen-binding assay
- Factor VIII clotting activity

Screening tests for bleeding disorders (such as aPTT and bleeding time) can be normal in mild disease. Stress, pregnancy, or medications (e.g., oral contraceptives) can falsely elevate vWF levels in a patient. Once a diagnosis of vWF deficiency is suspected, vWF multimer analysis or genetic testing may assist in defining the subtype of vWF deficiency.

Cooper S, Takemoto C. Von Willebrand disease. *Pediatr Rev.* 2014;35(3):136–137.

32. What does the ristocetin cofactor assay measure?

vWF activity. vWF will bind to the glycoprotein IB receptor on platelets in the presence of the antibiotic ristocetin. A patient's plasma is serially diluted and mixed with platelets. The presence of vWF allows for platelet agglutination, which can then be quantified on the basis of the dilutions.

33. How is von Willebrand disease treated?

Treatment depends on the variant of von Willebrand disease that is identified:

- *If protein is normal but diminished in quantity*, DDAVP is given to stimulate endogenous release. DDAVP is now available for intravenous use and for intranasal use (Stimate). It is important to test von Willebrand disease patients for the safety and efficacy of either form of DDAVP before clinical use. It is also important to distinguish the form of intranasal DDAVP used for vWF therapy from that used for enuresis management.
- *If protein is abnormal but bleeding is mild,* desmopressin may also be of value.
- *If protein is abnormal but bleeding is severe,* licensed vWF concentrates may be administered. Plasma-derived but highly purified products (trade names include Alphanate, Humate-P and Wilate) provide both vWF and factor VIII. The ristocetin cofactor activity is quantitated for each vial, which allows for more precise use. A recombinant product (trade name Vonvendi) is also approved for adults.

Sharma R, Flood VH. Advances in the diagnosis and treatment of von Willebrand disease. *Blood.* 2017;130(22):2386–2391.

34. In an adolescent with menorrhagia, how likely is a bleeding disorder?

Up to 20% may have a bleeding disorder, particularly von Willebrand disease. The American College of Obstetrics and Gynecology recommends screening for any patient $<$18 years with menorrhagia.

Graham RA, Davis JA, Corrales-Medina FF. The adolescent with menorrhagia: diagnostic approach to a suspected bleeding disorder. *Pediatr Rev.* 2018;39(12):588–600.

Kulp JL, Mwangi CN, Loveless M. Screening for coagulation disorders in adolescents with abnormal uterine bleeding. *J Pediatr Adolesc Gynecol.* 2008;21(1):27.

35. How does DDAVP work in the treatment of von Willebrand disease?

DDAVP is a synthetic analog of vasopressin, the antidiuretic hormone. Within 1 to 2 hours of its administration (either intravenous, subcutaneous, or intranasal), plasma vWF levels increase by two-fold to eight-fold. DDAVP appears to act by causing the release of vWF from the endothelial cells. Factor VIII levels also increase in part because of the increased stabilization of vWF/factor VIII complex by DDAVP, which lessens proteolytic degradation. As a caution, DDAVP administration in the setting of von Willebrand disease type IIB may cause a dangerous drop in platelet count due to increased vWF binding and platelet clearance.

36. Should children awaiting surgery undergo routine preoperative screening for potential abnormal bleeding?

This is controversial. Studies have shown that the frequency of abnormal screening testing is low, around 2%. Most of the abnormalities identified were transient and unlikely to be clinically significant. In the absence of symptoms and a negative family history, the diagnosis of a bleeding disorder is unlikely. However, others argue that screening should be used despite the small yield to avoid missing an undiagnosed bleeding disorder.

Nieto RM, De Leon LE, Diaz DT, et al. Routine preoperative laboratory testing in elective cardiothoracic surgery is largely unnecessary. *J Thorac Cardiovasc Surg.* 2017;153(3):678–685.

Shah MD, O'Riordan MA, Alexander SW. Evaluation of prolonged aPTT values in the pediatric population. *Clin Pediatr.* 2006;45(4): 347–353.

Burk CD, Miller L, Handler SD, et al. Preoperative history and coagulation screening in children undergoing tonsillectomy. *Pediatrics.* 1992;89(4 Pt 2):691.

37. What is the role of vitamin K in coagulation?

Vitamin K is essential for the γ-carboxylation of both procoagulants (including factors II, VII, IX, and X) and anticoagulants (proteins C and S). γ-carboxylation occurs in the liver and converts the proteins to their functional forms. Vitamin K is obtained in three ways: (1) as dietary fat-soluble K1 (phytonadione) from leafy vegetables and fruits, (2) as K2 (menaquinone) from synthesis by intestinal bacteria, and (3) as water-soluble K3 (menadione) from commercial synthesis.

38. In what settings outside the newborn period can vitamin K abnormalities contribute to a bleeding diathesis?

- **Malabsorptive intestinal disorders** (e.g., cystic fibrosis, Crohn disease, short-bowel syndrome)
- **Prolonged antibiotic therapy** (this diminishes intestinal bacteria)
- **Prolonged hyperalimentation without supplementation**
- **Malnutrition**
- **Chronic hepatic disorders** (hepatitis, α_1-antitrypsin deficiency) can diminish both the absorption of fat-soluble vitamin K (as a result of diminished bile salt production) and the use of vitamin K in factor conversion
- **Drugs** that can disrupt vitamin K include phenobarbital, phenytoin, rifampin, and Coumadin

39. What is the best test for distinguishing coagulation disturbances that result from hepatic disease, DIC, and vitamin K deficiency?

Factors II, V, VII, IX, and X are made in the liver, and all of these factors (except factor V) are vitamin K dependent. Therefore the measurement of **factor V** is a useful test to distinguish liver disease from vitamin K deficiency because this factor is reduced in the former and normal in the latter disorder. Factor VIII is reduced in patients with DIC because of the consumptive process, but this factor is normal or increased in patients with liver disease and vitamin K deficiency. Therefore the **factor VIII** level is a good test to distinguish DIC from the other two disorders (Table 9.2).

Table 9.2 Coagulation Abnormalities in Liver Disease, Vitamin K Deficiency, and Disseminated Intravascular Coagulation

	FACTOR V	FACTOR VII	FACTOR VIII
Liver disease	Low	Low	Normal or increased
Vitamin K deficiency	Normal	Low	Normal
Disseminated intravascular coagulation	Low	Low	Low

40. What is DIC?

DIC is an acquired syndrome that is precipitated by a variety of diseases and characterized by diffuse fibrin deposition in the microvasculature, consumption of coagulation factors, and endogenous generation of thrombin and plasmin. The process is uncontrolled, and the result can be significant microthrombus formation with ischemic injury to multiple organ systems.

41. What tests are valuable for the diagnosis of suspected DIC?

See Table 9.3.

Table 9.3 Tests for Diagnosis of Disseminated Intravascular Coagulation

TEST	USUAL RESULTS
Prothrombin time; activated partial thromboplastin time	Prolonged
Fibrinogen	<100 mg/dL*
Platelet count	Low
D-Dimer	>2 µg/mL
Factors II, V, and VIII	Usually low*

*These results may be normal, however, especially in patients with mild disseminated intravascular coagulation because synthesis increases with accelerated consumption.

Data from Nathan DG, Orkin SH, Ginsburg D, Look AT, eds. *Nathan and Oski's Hematology of Infancy and Childhood.* 6th ed. Philadelphia, PA: W.B. Saunders; 2003:1524.

42. What is the treatment of choice for DIC?

DIC occurs most commonly in the context of bacterial sepsis and hypotension. The best treatment is reversal of the underlying cause through treatment of the infection and appropriate fluid and pressor management. If bleeding is severe or if hemorrhage is occurring in a life-threatening location, platelets and fresh frozen plasma (FFP) should be given to make up for the loss of these elements, which is occurring from consumption. Heparin has not been proven to be effective for increasing survival in patients with sepsis and DIC. The replenishment of depleted antithrombin III levels with antithrombin III concentrate may decrease the risk for new thromboses. Supplementation with prothrombin complex concentrates (aPCCs), recombinant protein C, and thrombomodulin has been trialed in adults and pediatric patients with DIC but have not shown a clear clinical benefit.

Rajagopal R, Thachil J, Monagle P. Disseminated intravascular coagulation in paediatrics. *Arch Dis Child.* 2017;102(2):187–193.

43. What are the common hereditary disorders that predispose a child to thrombosis?

- **Factor V Leiden:** This is an abnormal factor V protein that is resistant to the normal antithrombotic effect of activated protein C.
- **Protein C deficiency:** Protein C inactivates factors V and VIII and stimulates fibrinolysis.
- **Protein S deficiency:** Protein S serves as a cofactor for the activity of protein C.
- **Antithrombin III deficiency:** Antithrombin III is involved in the inhibition of thrombin; factor X; and, to a lesser extent, factor IX.
- **Prothrombin variation:** Mutation at gene position 20210 increases prothrombin levels possibly through decreased messenger RNA (mRNA) degradation.
- **Hyperhomocysteinemia:** Can be the result of a variant of the *MTHFR* gene, but the level of homocysteine needs to be elevated for the variant to play a role. Those with predisposition to hyperhomocysteinemia due to thermolabile *MTHFR* variants benefit from folate supplementation, sometimes with vitamins B_6 and B_{12} in addition.
- **Antiphospholipid antibodies:** These are passed from mother to infant prenatally. They can also be acquired, often in adolescence, in the presence of systemic autoimmune diseases such as systemic lupus erythematosus (SLE).

Yang JY, Chan AK. Pediatric thrombophilia. *Pediatr Clin North Am.* 2013;60(6):1443–1462.

44. What are the inheritance patterns of the hypercoagulable states?

Factor V Leiden, protein C deficiency, protein S deficiency, and *antithrombin III deficiency* are all inherited in an **autosomal dominant** pattern. Factor V Leiden is transmitted with incomplete penetrance. The factor V Leiden mutation is present in 3% to 6% of Caucasian children, and evidence indicates that some of these heterozygous individuals are at increased risk for venous thrombosis, especially when combined with other risk factors. Nearly 200 pathogenic mutations in the *PROC* gene have been described for protein C deficiency. Protein S deficiency is due to mutations in the *PROS1* gene. Mutations in the *SERPINC1* gene are responsible for antithrombin III abnormalities.

45. In an adolescent with an unprovoked deep vein thrombosis (DVT), what risk factors need to be assessed?

In young patients with a spontaneous DVT (not line-associated), one main concern is an inherited thrombophilia. Adolescents with unprovoked DVTs may have an inherited condition; however, they may also have additional modifiable risk factors that predispose them to DVTs, such as the use of estrogen-containing birth control pills, smoking, driving/sitting for prolonged periods, excessive repetitive motions, and pregnancy. Autoimmune phenomena, including antiphospholipid antibody syndrome, also are increased in frequency in adolescents and should be evaluated.

46. What anatomic variants will predispose individuals to venous thromboses?

- **May-Thurner syndrome** is an anatomic variant where the left common iliac vein is compressed by the right common iliac artery, causing venous outflow tract obstruction and predisposing patients to DVTs in the left lower extremity.
- **Paget-Schroetter disease** is a form of upper extremity DVT in the axillary or subclavian veins due to extrinsic compression or repetitive injury as the subclavian vein passes by the junction of the first rib and the clavicle. This is also called "effort thrombosis," as athletes (particularly pitchers) and violin players are susceptible.

47. What are the mechanisms for low-molecular-weight heparin (LMWH) and pentasaccharide as antithrombotic agents?

- *LMWH* is the sulfated oligosaccharide heparin, derived from natural sources such as beef lung and pig intestine, that has been subjected to heparinase treatment to reduce the average molecular weight. Dosing and bioavailability are standardized, with less frequent or no monitoring of the anti–factor Xa activity, depending on clinical circumstances. LMWH still works by binding antithrombin to enhance its anti–factor IIa and anti–factor Xa activities.

- *Pentasaccharide (Fondaparinux)* is a synthetic five-sugar agent that binds antithrombin and primarily inhibits factor Xa. It has a longer half-life and reduced monitoring advantages over heparin, but currently no antidote is available clinically.

Radulescu VC. Anticoagulation therapy in children. *Semin Thrombo Hemost.* 2017;43(8):877–885.

48. What are the two classes of direct oral anticoagulants?

- **Direct thrombin inhibitors (DTIs)** are anticoagulant drugs that block the enzymatic activity of thrombin, the final enzyme of the clotting cascade, which cleaves fibrinogen to fibrin. Unlike heparin, which enhances the activity of antithrombin as a mechanism of action, DTIs bind directly to thrombin. DTIs can be given parenterally or orally, such as dabigatran, and are usually cleared by the liver. Use in children is reserved for conditions in which heparin is contraindicated, such as heparin-induced thrombocytopenia (HIT).
- **Direct factor Xa inhibitors** affect coagulation earlier in the cascade by preventing factor Xa from cleaving prothrombin to thrombin. These are oral agents and include apixaban (Eliquis) and rivaroxaban (Xarelto). In adults, they are effective in treatment and secondary prevention of thrombosis and rarely need monitoring.

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von Vajna E, Alam R, So T-Y. Current clinical trials on the use of direct oral anticoagulants in the pediatric population. *Cardiol Ther.* 2016;5(1):19–41.

DEVELOPMENTAL IMMUNOLOGY

49. Which are the characteristics of immunoglobulin (Ig) transport across the placenta?

IgG is the only isotype that is transferred across the placenta. All IgG subclasses cross the placenta, and their relative concentrations in the cord serum are comparable with those of the maternal serum. Transfer of IgG can first be detected as early as 8 weeks of gestation, and levels rise steadily between 18 and 22 weeks. By 30 weeks, the serum concentrations of IgG are about 50% of those observed in neonates born at term. IgG concentrations comparable with those of the mother are achieved by 34 weeks of gestation, and values at term can be higher by about 10% compared with maternal serum levels as a result of the active transport across the placenta.

50. How do Ig levels change during the first years of life?

- IgG levels in a full-term baby are equal or higher (5% to 10%) than maternal levels as a result of active placental transport. With an IgG half-life of 21 days, this transported maternal IgG reaches a nadir after 3 to 5 months. As the infant begins to make IgG, the level begins to rise slowly; it is 60% of the adult level at 1 year of age, and it achieves the adult level by 6 to 10 years of age.
- Immunoglobulin M (IgM) concentrations are normally very low at birth, and 75% of normal adult concentrations are usually achieved by about 1 year of age.
- Immunoglobulin A (IgA) is the last Ig produced and approaches 20% of adult value by 1 year; however, full adult levels are not reached until adolescence. Because delays in the production of IgA are not unusual, the diagnosis of IgA deficiency is difficult to make with certainty in a child who is younger than 2 years.
- Immunoglobulin D (IgD) and immunoglobulin E (IgE), both of which are present in low concentrations in the newborn, reach 10% to 40% of adult concentrations by 1 year of age.

51. Why are antibodies not produced by the fetus in appreciable quantities?

- The fetus is in a sterilel or semisterile environment and is not exposed to foreign antigens.
- The active transport of maternal IgG across the placenta may suppress fetal antibody synthesis.
- Fetal and neonatal monocyte-macrophages may not process foreign antigens normally.

52. What is the role of the thymus?

The *thymus* is the primary lymphoid organ for the production and generation of T cells bearing the α/β T-cell antigen receptor. The thymus is responsible for the central selection of the T-cell repertoire, which allows for the establishment of tolerance toward self-antigens and responsiveness to nonself (i.e., foreign) antigens.

53. At what age does thymic function cease?

At birth, the thymus is at two-thirds of its mature weight, and it reaches its peak mass at about 10 years of age. Subsequently, thymic size declines, but substantial function (as measured by the output of new T cells) persists into very late adulthood (70 to 80 years of age).

54. How does neutrophil function in the neonate compare with that of adults?

There is a diminished neutrophil storage in the neonate, and the cells display a reduced adhesion and migration capacity in response to chemotactic stimuli. By contrast, the efficiency for the ingestion and killing of bacteria is normal for these cells. Under suboptimal conditions, however, these effector functions may be diminished, and neutrophils from sick and stressed neonates can display a decreased microbicidal activity.

HEMATOLOGY LABORATORY

55. Of the seven RBC parameters given by a Coulter counter, which are measured and which are calculated?

The Coulter counter, which is the most commonly used automated electronic cell counter, uses the impedance principle. A precise volume of blood passes through a narrow aperture and impedes an electrically charged field, and each "blip" is counted as a cell. The larger the RBC, the greater the electric displacement. In a separate chamber, the same volume is hemolyzed and colorimetrically analyzed to determine hemoglobin concentration.

Measured values

- RBC count
- Mean corpuscular volume (MCV)
- Hemoglobin (Hb)

Calculated values

- Mean corpuscular hemoglobin (MCH, measured in pg/cell) $= (10 \times [\text{Hb} / \text{RBC}])$
- Mean corpuscular hemoglobin concentration (MCHC, measured in g/dL) $= (100 \times [\text{Hb} / \text{Hct}])$
- Hematocrit (Hct, given as a percentage) $= (\text{RBC} \times [\text{MCV} / 10])$
- RBC distribution width (RDW) = coefficient of variation in RBC size

56. How does the MCV help provide a quick screen of the possible causes of anemia?

- **Microcytic:** iron deficiency, thalassemias, sideroblastic anemia
- **Normocytic:** autoimmune hemolytic anemia (AIHA), hemoglobinopathies, enzyme deficiencies, membrane disorders, anemia of chronic inflammation
- **Macrocytic:** disorders of B_{12} and folic acid metabolism, bone marrow failure

57. What is a quick rule of thumb for approximating the lower limit of MCV?

70 + (age in years). This number (in mm^3) approximates the lower limit of MCV in children <12 years old, below which microcytosis is present. After the age of 12 years, the lower limit for normal MCV is 82 fL. The MCV is higher in newborn infants and varies inversely with gestational age. In a newborn infant, the lower limit of MCV is 94 fL.

58. In addition to an elevated reticulocyte count, what laboratory studies suggest increased destruction (rather than decreased production) of RBCs as a cause of anemia?

- **Increased serum erythrocyte lactate dehydrogenase:** More commonly seen in patients with hemolytic diseases, it can be greatly elevated in patients with ineffective erythropoiesis (e.g., megaloblastic anemia).
- **Decreased serum haptoglobin:** When RBCs lyse, serum haptoglobin binds the released hemoglobin and is excreted. However, up to 2% of the population has congenitally absent haptoglobin.
- **Hyperbilirubinemia (indirect):** This is usually increased with RBC lysis. However, it may also be elevated in patients with ineffective erythropoiesis (e.g., megaloblastic anemia). Additionally, 3% to 7% of the Caucasian population has Gilbert disease, which can cause intermittent indirect hyperbilirubinemia in the setting of physiologic stresses (fasting, illness, vigorous exercise) due to a defect in the hepatic processing of bilirubin.

59. Why must the reticulocyte count sometimes be corrected?

Because the reticulocyte count is expressed as a percentage of total RBCs, it must be adjusted for the degree of anemia with the following formula: reticulocyte % × (patient Hct / normal Hct) = corrected reticulocyte count. For example, a very anemic 10-year-old patient with a hematocrit level of 7% (in contrast with an expected normal hematocrit of 36%) and a reticulocyte count of 5% has a corrected reticulocyte count of 1.0%: $5\% \times (7\%/36\%) = 1\%$. This is not appropriately elevated, as might be seen in patients with severe iron deficiency. The key concept is the appropriateness of the reticulocyte response to anemia. The corrected "retic count" should be elevated if the bone marrow is working properly and has all the right nutrients for making RBCs, including iron, folate, and vitamin B_{12}.

60. In what settings of shortened RBC survival can the reticulocyte count be normal or decreased?

As a rule, the reticulocyte count is elevated in conditions of shortened RBC survival (e.g., hemoglobinopathies, membrane disorders, immune hemolysis) and decreased in anemias that are characterized by impaired RBC production (e.g., iron deficiency, aplastic anemia). The reticulocyte count may be unexpectedly low in a setting of shortened RBC survival in the following conditions:

- Aplastic or hypoplastic crisis is occurring at the same time, as is seen in patients with human parvovirus B19 infection.
- An autoantibody in immune-mediated hemolysis reacting with antigens that are present on reticulocytes leads to increased clearance of these cells.
- In patients in chronic states of hemolysis, the marrow may become unresponsive as a result of micronutrient deficiency (e.g., iron, folate) or because of a reduction in erythropoietin production, as is seen in patients with chronic renal failure.

61. What is the significance of targeting on an RBC smear?

RBC targets on a peripheral smear are caused by excessive membrane relative to the amount of hemoglobin. Therefore *target cells* (Fig. 9.2) are found when the **membrane is increased** (e.g., in patients with liver disease) **or** when the **intracellular hemoglobin is diminished** in smaller RBC volumes (e.g., in patients with iron deficiency or thalassemia trait). Target cells may also be found in patients with certain hemoglobinopathies (e.g., hemoglobins C and SC). In these instances, the target cells are caused by aggregation of the abnormal hemoglobin.

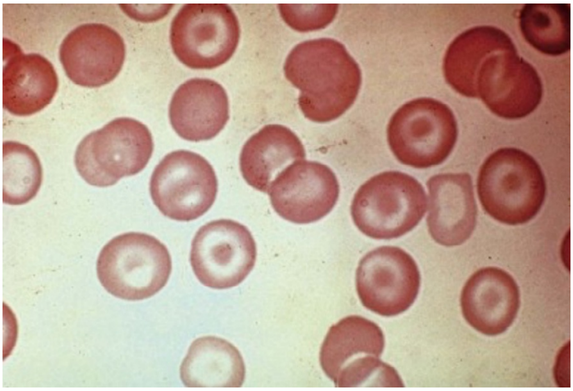

Fig. 9.2 Target cells in obstructive liver disease. In contrast to the target cells in hypochromic-microcytic anemias, the target cells in liver disease are normal in size and well hemoglobinized. (From Orkin SH, Fisher DE, Ginsburg D, et al, eds. *Nathan and Oske's Hematology and Oncology of Infancy and Childhood.* 8th ed. Philadelphia, PA: Elsevier; 2015:576.)

62. In what conditions are Howell-Jolly bodies found?

Howell-Jolly bodies are nuclear remnants that are found in the RBCs of patients with reduced or absent splenic function (e.g., sickle cell disease, heterotaxy) and in patients with megaloblastic anemias. They are occasionally present in the RBCs of premature infants. These remnants are part of the process of normal RBC maturation but are typically removed by a normal spleen. Howell-Jolly bodies are dense, dark, and perfectly round, and their characteristic appearance makes them easily distinguishable from other RBC inclusions and from platelets overlying RBCs (Fig. 9.3).

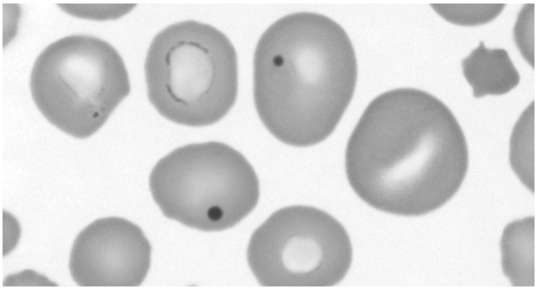

Fig. 9.3 Red blood cells with Howell-Jolly bodies in a patient with hyposplenism. The cytoplasmic inclusions are nuclear remnants. (From Hoffman R, Benz EJ Jr, Silberstein LE, et al, eds. *Hematology: Basic Principles and Practice.* 6th ed. Philadelphia, PA: Elsevier; 2013:2259.)

63. What is the cause of Heinz bodies?

Heinz bodies represent precipitated denatured hemoglobin in the RBC. Heinz bodies occur when the hemoglobin is intrinsically unstable (e.g., hemoglobin Koln) or when the enzymes that normally protect hemoglobin from oxidative denaturation are abnormal or deficient (e.g., glucose-6-phosphate-dehydrogenase [G6PD] deficiency). These inclusions are not visible with a routine Wright-Giemsa stain but can be readily seen with methyl violet or brilliant cresyl blue stains.

64. What makes an "atypical lymphocyte" atypical?

Atypical lymphocytes (Fig. 9.4) are young lymphocytes (not lymphoblasts) that are characterized by an irregular plasma membrane with a large nucleus. Cytoplasm is typically basophilic. On a blood smear, where an atypical lymphocyte abuts an RBC, the shape of the lymphocyte will deform around it. Atypical lymphocytes are seen in a variety of illnesses, most commonly infectious mononucleosis.

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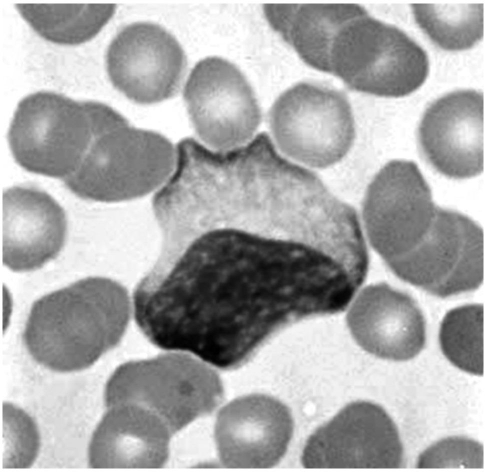

Fig. 9.4 Atypical lymphocyte. Note the deformation of the lymphocyte by the adjacent red cells. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis.* 5th ed. Philadelphia, PA: Mosby; 2007:421.)

65. A patient with oculocutaneous albinism has repeated *Staphylococcus aureus* infections and the peripheral smear shown in Fig. 9.5. What is the likely diagnosis?

Chédiak-Higashi syndrome. This is an autosomal recessive disease with a defect in phagocytosis due to a mutation of a lysosomal trafficking regulator protein. Microtubules do not form normally, and neutrophils do not respond to chemotactic stimuli. *Giant lysosomal granules,* which fail to function properly, are evident in a peripheral smear. Associated features include partial albinism, peripheral neuropathy, and a susceptibility to recurrent pyogenic infections.

Kaplan J, De Domenico I, Ward DM. Chediak-Higashi syndrome. *Curr Opin Hematol.* 2008;15(1):22–29.

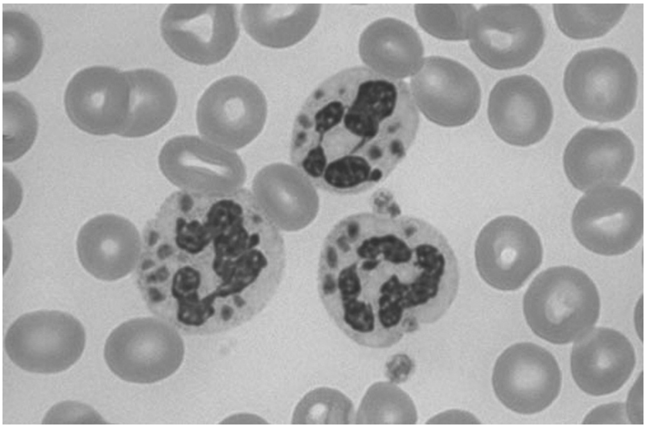

Fig. 9.5 Chédiak-Higashi syndrome, microscopic peripheral blood smear demonstrating giant lysosomal granules in the white blood cells. (From Klatt EC. *Robbins and Cotran Atlas of Pathology.* 2nd ed. Philadelphia, PA: Saunders Elsevier; 2010:67.)

66. What is the hemoglobin value below which children are considered to be anemic (lower limit of normal)?

- Newborn (full term): 13.0 g/dL
- 3 months: 9.5 g/dL
- 1 to 3 years: 11.0 g/dL
- 4 to 8 years: 11.5 g/dL
- 8 to 12 years: 11.5 g/dL
- 12 to 16 years: 12.0 g/dL

Dallman P, Siimes MA. Percentile curves for hemoglobin and red-cell volume in infancy and childhood. *J Pediatr.* 1979;94(1):26–31.

67. When does physiologic anemia of infancy occur?

Physiologic anemia occurs at **8 to 12 weeks in full-term infants** and at **6 to 8 weeks in premature infants**. Full-term infants may exhibit hemoglobin levels as low as 9 g/dL at this time, and very premature infants may have levels as low as 7 g/dL. The mechanisms responsible for physiologic anemia are not completely understood. RBC survival time is decreased in both premature and full-term infants. Furthermore, the ability to increase endogenous erythropoietin production is somewhat blunted, although the response to exogenous erythropoietin is normal. Lastly, the hemoglobin concentration appears lower because the plasma volume increases with growth during that period of life without a similar increase in the hemoglobin concentration (i.e., there is a dilutional effect).

68. How does the pathophysiology of anemia differ in chronic and acute infection?

- *Chronic infection* and other inflammatory states impair the release of iron from reticuloendothelial cells, thereby decreasing the amount that is available for RBC production. The lack of mobilizable iron may result from the action of proinflammatory cytokines (e.g., interleukin-1 [IL-1], tumor necrosis factor [TNF]-α). Giving additional iron under these circumstances further increases reticuloendothelial iron stores and does little to help the anemia.
- *Acute infection* may cause anemia through a variety of mechanisms, including bone marrow suppression, shortened RBC life span, RBC fragmentation, and immune-mediated RBC destruction.

69. What is the differential diagnosis for children with anemia and splenomegaly?

Key question: Is the anemia the cause of the splenomegaly, or is the splenomegaly the cause of the anemia?

Anemia-causing splenomegaly

- Membrane disorders
- Hemoglobinopathies
- Enzyme abnormalities
- Immune hemolytic anemia

Splenomegaly-causing anemia

- Cirrhotic liver disease
- Cavernous transformation of portal vessels
- Storage diseases
- Persistent viral infections

70. What is the significance of a leukemoid reaction?

A *leukemoid reaction* usually refers to a WBC count of $>$50,000/mm^3 and an accompanying shift to the left (i.e., the differential count shows an increase in immature cells). Causes include bacterial sepsis, pertussis, tuberculosis, congenital syphilis, congenital or acquired toxoplasmosis, and erythroblastosis fetalis.

71. Name the three most common causes of eosinophilia in children in the United States.

Eosinophilia, which is usually defined as more than 10% eosinophils or an absolute eosinophil count of 1000/mm^3 or greater, is most commonly seen in three atopic conditions: **atopic dermatitis**, **allergic rhinitis**, and **asthma**.

72. What conditions are associated with extreme elevations of eosinophils in children?

- Visceral larval migrans (toxocariasis)
- Other parasitic disease (trichinosis, hookworm, ascariasis, strongyloidiasis)
- Eosinophilic leukemia
- Hodgkin disease
- Drug hypersensitivity
- Idiopathic hypereosinophilic syndrome

73. A 14-month-old child presents with symptoms including marked cyanosis, lethargy, and normal oxygen saturation by pulse oximetry after drinking from a neighbor's well. What is the likely diagnosis?

Methemoglobinemia should always be considered when a patient presents symptoms of cyanosis without demonstrable respiratory or cardiac disease. Methemoglobin is produced by the oxidation of ferrous iron in hemoglobin into ferric iron. Methemoglobin cannot transport oxygen. Normally, it constitutes $<$2% of circulating hemoglobin. Oxidant toxins (e.g., antimalarial drugs, nitrates in food or well water) can dramatically increase the concentration. Patients with cyanosis as a result of methemoglobinemia can have normal oxygen saturation as measured by pulse oximetry because the oximeter operates by measuring only hemoglobin that is available for saturation.

74. What is the treatment for methemoglobinemia?

In an acute situation in which levels of methemoglobin are $>$30%, treatment consists of 1 to 2 mg/kg of 1% methylene blue administered intravenously over 5 minutes and repeated in 1 hour if levels have not fallen to normal. Failure to respond to therapy should raise the possibility of G6PD deficiency, which prevents the conversion of methylene blue to the metabolite that is active in the treatment of methemoglobinemia. In these cases, hyperbaric oxygen therapy or exchange transfusion may be necessary.

Cortazzo JA, Lichtman AD. Methemoglobinemia: a review and recommendations for management. *J Cardiothorac Vasc Anesth*. 2014; 28(4):1043–1047.

75. Why are infants at greater risk for the development of methemoglobinemia?

- **Antioxidant defense mechanisms** (e.g., soluble cytochrome *b*5 and nicotinamide adenine dinucleotide hydrogen (NADH)–dependent cytochrome *b*5 reductase) are 40% lower in infants than in teenagers.
- An infant's **intestinal pH** is relatively alkaline compared with that of older children. If nitrates are ingested (e.g., from fertilizer-contaminated well water), this higher pH more readily allows bacterial conversion of nitrate to nitrite, which is a potent oxidant.
- Infants are **more susceptible** to various oxidant exposures: nitrate reductase from foods such as undercooked spinach, menadione (vitamin K_3) for the prevention of neonatal hemorrhage, over-the-counter teething preparations with benzocaine, and metoclopramide for gastroesophageal reflux.

Bunn HF. Human hemoglobins: normal and abnormal. In Nathan DG, Orkin SH, eds. *Nathan and Oski's Hematology of Infancy and Childhood.* 5th ed. Philadelphia, PA: W.B. Saunders; 1998:729.

HEMOLYTIC ANEMIA

76. What clinical features are suspicious for hemolytic anemia?

- Discolored urine (dark, brown, red)
- Jaundice
- Pallor
- Tachycardia
- Splenic and/or liver enlargement
- If very severe, hypovolemic shock or congestive heart failure

77. What two types of RBC forms are commonly seen on the peripheral smear in patients with hemolytic anemia?

- **Spherocytes or microspherocytes:** These forms can be seen in any hemolytic anemia that results from a loss of RBC membrane surface area (e.g., Coombs-positive hemolytic anemia, DIC, or hereditary spherocytosis).
- **Schistocytes:** These are various configurations of fragmented RBCs (Fig. 9.6), which can be seen in patients with microangiopathic hemolytic anemia, a form of intravascular hemolysis caused by mechanical disruption (e.g., prosthetic heart valves, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, cavernous hemangioma). Schistocytes are also seen in patients with severe burns and DIC.

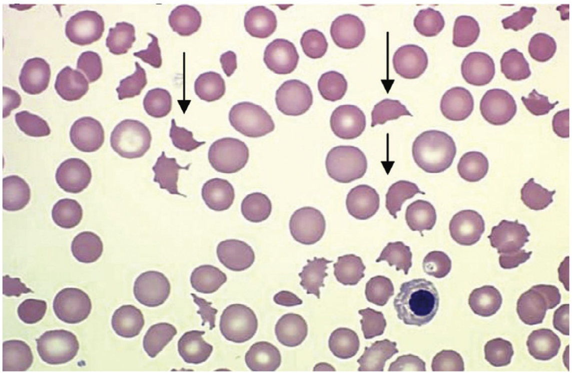

Fig. 9.6 Schistocytes *(arrows)* in the peripheral smear of a patient with microangiopathic hemolytic anemia. (From Carey WD, ed. *Current Clinical Medicine.* 2nd ed. Philadelphia, PA: Elsevier Saunders; 2010:579.)

78. What are the two most common inherited disorders of RBC membranes?

- **Hereditary spherocytosis** is characterized by hemolysis (anemia, reticulocytosis, jaundice, splenomegaly); spherocytosis; and, in most cases, a family history of hemolytic anemia, early gallstones, or splenectomy. The diagnosis can be made by establishing the presence of the clinical findings and by the finding of increased osmotic fragility of the RBCs. Hereditary spherocytosis is inherited as an autosomal dominant disorder about 75% of the time.
- **Hereditary elliptocytosis** is characterized by variable hemolysis, with a predominance of elliptocytes on the blood smear. It is usually inherited in an autosomal dominant pattern.

79. Which disorder is most commonly associated with an elevated MCHC?

Hereditary spherocytosis. The hyperchromic appearance of spherocytes and microspherocytes is the result of the loss of surface membrane, an excess of hemoglobin, and mild cellular dehydration. In other hemolytic anemias that feature spherocytosis, the percentage of spherocytes is usually insufficient to raise the MCHC.

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80. What is the osmotic fragility test?

This is a test to confirm the diagnosis of hereditary spherocytosis. A normal RBC is discoid in shape as a result of its relative excess of surface area per cell volume from the redundancy of its cell membrane. In increasingly hypotonic solutions, more and more RBCs will swell and burst at a standard rate. In spherocytosis, because there is less surface area to cell volume, more cells burst compared with normal in these hypotonic solutions, particularly after incubating at 37°C for 24 hours. This tendency toward earlier lysis makes them osmotically fragile (Fig. 9.7). Novel tests utilizing flow cytometric techniques and the eosin 5-maleimide (EMA) binding assay have also proven useful in the diagnosis of hereditary spherocytosis.

Ciepiela O. Old and new insights into the diagnosis of hereditary spherocytosis. *Ann Transl Med*. 2018;6(17):339.

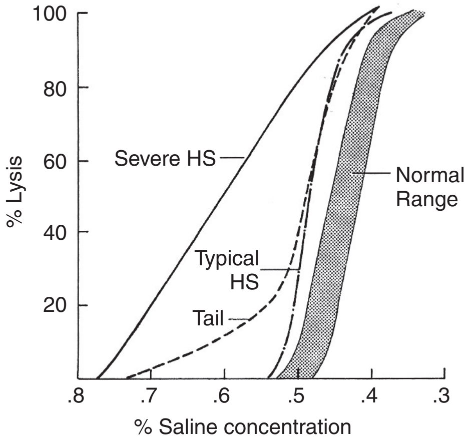

Fig. 9.7 Osmotic fragility curves in hereditary spherocytosis (HS). (From Nathan DG, Orkin SD, Ginsburg D, Look AT, eds. *Nathan and Oski's Hematology of Infancy and Childhood.* 6th ed. Philadelphia, PA: W.B. Saunders; 2003:610.)

81. What is the difference between alloimmune and autoimmune hemolytic anemia?

- *Alloimmune hemolytic anemia:* Antibodies responsible for hemolysis are directed against another's RBCs; it may cause acute or delayed hemolytic reactions.
- *Autoimmune hemolytic anemia (AIHA):* Antibodies are directed against the host's RBCs.

82. In which settings do alloimmune and AIHA most commonly appear?

Alloimmune: RBC antigen incompatibility between mother and fetus, transfusion of incompatible blood

Autoimmune:

- *Primary:* AIHA
- *Secondary:*
  - Infections (e.g., *Mycoplasma pneumoniae*, EBV, varicella, viral hepatitis)
  - Drugs (e.g., antimalarials, penicillin, tetracycline)
  - Systemic autoimmune disorders (e.g., SLE, dermatomyositis)

83. How does the cause of AIHA vary by age?

AIHA in children $<$10 years old is more likely to be *primary*. In children $>$10 years old, AIHA is more likely to be *secondary* to an underlying disease.

84. What is the most important test to establish the diagnosis of AIHA?

Direct Coombs test, also known as **direct antiglobulin test (DAT)**. The diagnosis of AIHA requires the presence of autoantibodies that bind to erythrocytes and signs or symptoms of hemolysis. However, approximately 10% of patients with AIHA are Coombs negative. Thus patients should be treated for AIHA if the disease is strongly suspected, even if the direct Coombs test is negative.

85. What are the differences between AIHAs caused by "warm" and "cold" erythrocyte autoantibodies?

- *Warm* (usually IgG antibodies with maximum activity at 37°C): These are most commonly directed against the Rh antigens and generally do not require complement for in vivo hemolysis. Hemolysis is predominantly *extravascular*—consumption occurs primarily in the spleen. Warm antibody-mediated hemolytic anemia is more likely to be associated with underlying disease (especially SLE in females) and to become chronic. Splenectomy and/or immunosuppression (e.g., with steroids) are often effective therapies.

- *Cold* (IgM antibodies with maximum activity between 0° and 30°C): These are most commonly directed against I or i antigen. Hemolysis is most commonly *intravascular* via complement activation. Extravascular hemolysis that does occur primarily involves hepatic consumption. Cold antibody-mediated hemolytic anemia is more commonly associated with acute infection (e.g., *Mycoplasma pneumoniae*, EBV, CMV). Patients are less likely to develop chronic hemolysis, and therapy (e.g., splenectomy, immunosuppression) is often ineffective.

86. A 6-year-old presents with acute anemia, fatigue, jaundice, and dark urine after an early spring swim in a local quarry. What is the likely diagnosis?

Paroxysmal cold hemoglobinuria is a transient autoimmune hemolysis due to a Donath-Landsteiner (D-L) antibody. This may be challenging to diagnose because the D-L antibody is a biphasic hemolysin that attaches to the RBC membrane at cold temperatures and initiates the complement cascade. Once the RBCs are warmed by the body, the D-L antibody falls off, but the cells continue to lyse. The Coombs test is often negative. Significant hemolysis occurs after exposure to cold (such as swimming in an unheated body of water). The antibody is often triggered by a preceding infection. Treatment consists of warming the patient and providing any blood products as needed.

Shanbhag S, Spivak J. Paroxysmal cold hemoglobinuria. *Hematol Oncol Clin North Am*. 2015;29(3):473–478.

87. An 8-year-old black male developed jaundice and very dark urine 24 to 48 hours after beginning nitrofurantoin for a urinary tract infection. What is the likely diagnosis?

G6PD deficiency is the most common hemolytic anemia caused by an RBC enzymatic defect. The enzyme G6PD is a key component of the pentose phosphate pathway, which ordinarily generates sufficient nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) to maintain glutathione in a reduced state (and to make it available for combating oxidant stresses). The deficiency is inherited in an X-linked recessive fashion. In patients who are deficient (most commonly those of African, Mediterranean, or Asian ancestry), oxidant stresses (particularly certain drugs) can result in hemolysis.

Luzzatto L, Nannelli C, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. *Hematol Oncol Clin North Am.* 2016;30(2):373–393.

88. Why are "bite cells" seen in patients with G6PD deficiency?

Bite cells are abnormally shaped RBCs with semicircular portions removed from the cell margin that give the appearance of a "bite" having been taken from the cell (Fig. 9.8). These cells are seen in hemolytic anemias and anemias involving an altered, denatured hemoglobin (Heinz bodies), such as G6PD deficiency. These are cleaved by macrophages in the spleen, which results in the abnormal appearance.

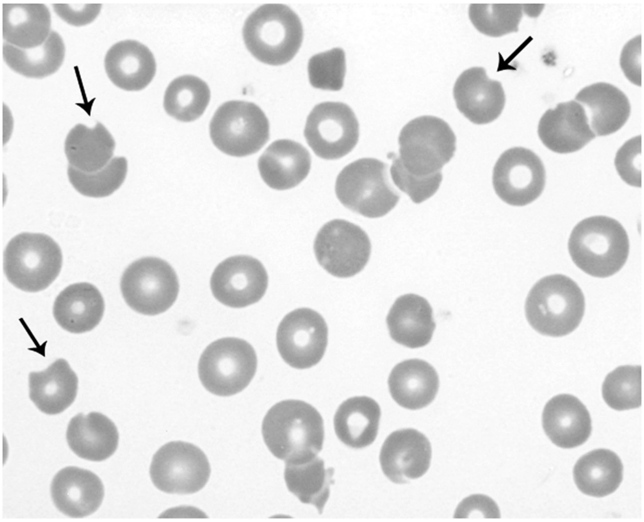

Fig. 9.8 Bite cells (arrows) in a patient with G6PD deficiency. (From Naeim F, Rao PN, Song SX, Grody WW, eds. *Atlas of Hematopathology.* London: Academic Press/Elsevier; 2013:698.)

89. In a patient with G6PD deficiency, why is the initial diagnosis often difficult in the acute setting?

The amount of G6PD enzymatic activity depends on the age of the RBC. Older RBCs have the least, and reticulocytes have the most. In an acute hemolytic episode, the older cells are destroyed first; younger ones may remain, and reticulocytes may increase. If erythrocytic G6PD levels are measured at this point, the result may be misleadingly near or above the normal range. If clinical suspicions remain, repeating the test when the reticulocyte count is reduced will give a more accurate measurement.

90. What is favism?

Favism refers to the clinical syndrome of acute hemolytic anemia from the ingestion of fava beans as an oxidative challenge in patients with G6PD deficiency. This is particularly common in portions of the Mediterranean and Asia, where fava beans are a dietary staple.

IMMUNODEFICIENCY

91. How is neutropenia defined?

Neutropenia is arbitrarily defined as an absolute neutrophil count (ANC) of $<1500/\text{mm}^3$. The ANC is determined by multiplying the percentage of bands and neutrophils by the total WBC count. An ANC of $<500/\text{mm}^3$ is severe neutropenia. Agranulocytosis is defined as an ANC of $<100/\text{mm}^3$. As a rule, the lower the ANC, the greater the risk for infectious complications.

92. How do children with neutrophil disorders present?

Neutrophil disorders include those that affect quantity (e.g., various neutropenias) and those that affect function (e.g., chemotaxis, phagocytosis, bactericidal activity). These defects should be considered part of the differential diagnosis in patients with delayed separation of the umbilical cord, recurrent infections with bacteria or fungi of low virulence (but minimal problems with recurrent viral or protozoal infections), poor wound healing, and specific locales of infection (e.g., recurrent furunculosis, perirectal abscesses, gingivitis).

93. What is the most common cause of transient neutropenia in children?

Viral infections, including influenza, adenovirus, Coxsackie virus, respiratory syncytial virus, hepatitis A and B, measles, rubella, EBV, CMV, and varicella. The neutropenia usually develops during the first 2 days of illness and may persist for up to a week. Multiple factors likely contribute to the neutropenia, including a redistribution of neutrophils (increased margination rather than circulation), sequestration in reticuloendothelial tissue, increased use in injured tissues, and marrow suppression. In general, otherwise healthy children with transient neutropenia as a result of viral infections are at low risk for serious infectious complications.

Dale DC. How I manage children with neutropenia. *Br J Haematol.* 2017;178(3):351–363.

94. Excluding intrinsic defects in myeloid stem cells, what conditions are associated with neutropenia in children?

- **Infection:** viral marrow suppression, bacterial sepsis-endotoxin suppression
- **Bone marrow infiltration:** leukemia, myelofibrosis
- **Drugs**
- **Immunologic factors:** neonatal alloimmune (secondary to maternal IgG directed against fetal neutrophils) and autoimmune neutropenia (e.g., autoimmune neutropenia of childhood, SLE, Evans syndrome)
- **Metabolic factors:** hyperglycinemia, isovaleric acidemia, propionic acidemia, methylmalonic acidemia, glycogen storage disease type IB
- **Nutritional deficiencies:** anorexia nervosa, marasmus, B_{12}/folate deficiency, copper deficiency
- **Sequestration:** hypersplenism

Dale DC. How I manage children with neutropenia. *Br J Haematol.* 2017;178(3):351–363.
Segel GB, Halterman S. Neutropenia in pediatric practice. *Pediatr Rev.* 2008;29(1):12–23.

95. Which is the most common form of chronic childhood neutropenia?

Autoimmune neutropenia of infancy and childhood (AIN). This disorder displays a 3:2 female predominance and is caused by a chronic depletion of mature neutrophils. About 90% of all cases are detected within the first 14 months of life. The median duration of neutropenia is 20 months, and 95% of patients with this condition have fully recovered by the time they are 4 years old. The ANC of infants with AIN is usually below $500/\text{mm}^3$, and the bone marrow displays normal cellularity despite an arrest at late stages of metamyelocytes or at the band stage. Antineutrophil antibodies are occasionally detected, but their presence is not necessary for the diagnosis of AIN.

Farruggia P, Dufour C. Diagnosis and management of primary autoimmune neutropenia in children: insights for clinicians. *Ther Adv Hematol.* 2015;6(1):15–24.

96. How common are primary immunodeficiencies?

- *Primary immune deficiencies:* 1:10,000 (excluding asymptomatic IgA deficiency)
- *B-cell defects:* 65%

- *Combined cellular and antibody deficiencies:* 15% (severe combined immunodeficiency: 1 in 100,000 newborns)
- *Phagocytic disorders:* 10%
- *T-cell–restricted deficiencies:* 5%
- *Complement component disorders:* 5%

In a survey study of 10,000 American households, the calculated prevalence of a diagnosed immunodeficiency was 1 in 2000 in children, 1 in 1200 in people of all ages, and 1 in 600 households.

Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. *J Clin Immunol.* 2007;27(5):497–502.

Immune Deficiency Foundation. www.primaryimmune.org. Accessed January 15, 2020.

International Patient Organization for Primary Immunodeficiencies. www.ipopi.org. Accessed January 15, 2020.

97. What are the typical clinical findings of the various primary immunodeficiencies?

See Table 9.4.

Ochs HD, Hagin D. Primary immunodeficiency disorders: general classification, new molecular insights and practical approach to diagnosis and treatment. *Ann Allergy Asthma Immunol.* 2014;112(6):489–495.

Table 9.4 Clinical Findings of Primary Immunodeficiencies

	PREDOMINANT B-CELL DEFICIENCY	PREDOMINANT T-CELL DEFICIENCY	PHAGOCYTIC DEFECTS	COMPLEMENT DEFECTS
Age at onset	After maternal antibodies have disappeared (usually >6 mo)	Early infancy	Early infancy	Any age
Type of infection	Gram-positive or gram-negative (encapsulated) bacteria, *Mycoplasma*, *Giardia*, *Cryptosporidium*, *Campylobacter*, enteroviruses	Viruses, particularly CMV-1 and CBV; systemic BCG after vaccination; fungal; *Pneumocystis carinii*	Gram-positive or gram-negative bacteria; catalase-positive organisms in CGD, especially *Aspergillus*	*Streptococcus*, *Neisseria*
Clinical findings	Recurrent respiratory tract infections, diarrhea, malabsorption, ileitis, colitis, cholangitis, arthritis, dermatomyositis, meningoencephalitis	Poor growth and failure to thrive, oral candidiasis, skin rashes, sparse hair, opportunistic infections, graft-versus-host disease, bony abnormalities, hepatosplenomegaly	Poor wound healing, skin diseases (e.g., seborrheic dermatitis, impetigo, abscess), cellulitis without pus, suppurative adenitis, periodontitis, liver abscess, Crohn disease, osteomyelitis, bladder outlet obstruction	Rheumatoid disorders, angioedema, increased susceptibility to infection

BCG, Bacille Calmette-Guérin; *CBV*, coxsackie B virus; *CGD*, chronic granulomatous disease; *CMV-1*, cytomegalovirus type 1.

98. What is the single most important laboratory test if severe combined immunodeficiency (SCID) is suspected?

A full blood count to document **lymphopenia** ($<2000/\text{mm}^3$) is the single most important laboratory test during the initial evaluation of a patient for suspected SCID. However, a minority of patients with SCID (about 20%) may have a normal absolute lymphocyte count.

99. Why are male children more likely to suffer from a primary immunodeficiency?

Several primary immunodeficiency disorders are linked to the X chromosome. These include agammaglobulinemia, hyper-IgM syndrome, SCID (the common cytokine receptor δ-chain deficiency), X-linked lymphoproliferative syndrome (XLP), Wiskott-Aldrich syndrome, one form of chronic granulomatous disease (CGD), and properdin deficiency. The male-to-female ratio is 4:1 among patients with a primary immunodeficiency who are younger than 16 years.

100. Which is the most common type of primary humoral immunodeficiency?

Selective IgA deficiency. The prevalence of selective IgA deficiency has been calculated to range from 1 in 220 to 1 in 3000, depending on the population studied. However, most IgA-deficient subjects remain healthy, which has been attributed to a compensatory increase of IgM in bodily secretions. A minority of these patients demonstrate normal levels of secretory IgA and normal numbers of IgA-bearing mucosal plasma cells. Although IgA represents less than 15% of total Ig, it is predominant on mucosal surfaces. Therefore most patients have recurrent diseases involving mucosal surfaces, including otitis media, sinopulmonary infections, or chronic diarrhea. Systemic infections are seen less frequently.

Koenen MH, van Montfrans JM, Sanders EAM, et al. Immunoglobulin A deficiency in children: an undervalued clinical issue. *Clin Immunol*. 2019;209:108293.

Yazdani R, Azizi G, Abolhassani H, Aghamohammadi A. Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. *Scand J Immunol*. 2017;85(1):3–12.

101. What are the diagnostic criteria for IgA deficiency?

Serum concentrations of IgA lower than 0.05 g/L are diagnostic and almost invariably associated with a concomitant lack of secretory IgA. Serum levels for IgM are normal, and concentrations for IgG (particularly IgG1 and IgG3) may be increased in one-third of all IgA-deficient patients.

102. What is the association between autoimmune disorders and IgA deficiency?

Autoimmune disorders have been described in **up to 40%** of patients with selective IgA deficiency. These include SLE, rheumatoid arthritis, thyroiditis, celiac disease, pernicious anemia, Addison disease, idiopathic thrombocytopenic purpura, and AIHA.

Yazdani R, Azizi G, Abolhassani H, Aghamohammadi A. Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. *Scand J Immunol*. 2017;85(1):3–12.

103. What are the allergies associated with IgA deficiency?

There is a strong association between IgA deficiency and allergic disorders. The most common diseases are allergic conjunctivitis, rhinitis, urticaria, atopic eczema, food allergies, and asthma.

National Institute of Allergy and Infectious Disease. www.niaid.nih.gov. Accessed January 15, 2020.

104. Why is Ig therapy not used as a treatment for selective IgA deficiency?

Unless a patient has a concurrent IgG subclass deficiency (even in this setting, therapy is controversial), γ globulin therapy is not indicated and is in fact relatively contraindicated because of the following:

- The short half-life of IgA makes frequent replacement therapy impractical.
- Gamma globulin preparations have insufficient IgA quantities to restore mucosal surfaces.
- Patients can develop anti-IgA antibodies with the potential for hypersensitivity complications, including anaphylaxis.

105. What gives common variable immunodeficiency (CVID) its variability?

CVID comprises a heterogeneous group of antibody deficiency syndromes due to differences in Ig production, in genetic defects, and in clinical manifestations. Estimates of its prevalence vary widely, from 1:5000 to 1:66,000. CVID is the most frequent *symptomatic* primary immunodeficiency in North America and Europe. (Primary IgA deficiency [see question 100] is more common but is often asymptomatic.) CVID is an immunodeficiency with defective Ig production, most commonly IgG with variable lower levels of IgM and/or IgA, due to impaired B-cell differentiation.

Abbott JK, Gelfand EW. Common variable immunodeficiency: diagnosis, management, and treatment. *Immunol Allergy Clin North Am.* 2015;35(4):637–658.

106. What are the clinical features of CVID?

Symptoms can vary from mild to severe based in part on the variability in Ig production. Recurrent infections of the respiratory tract (lungs, sinuses, ears) are the most common feature, often due to encapsulated bacteria and atypical bacterial pathogens, which can lead to chronic lung disease and bronchiectasis. GI complications with recurrent infections (including giardiasis, *Campylobacter jejuni*, *Helicobacter pylori*); inflammation and malabsorption; and accompanying symptoms of pain, vomiting, diarrhea, and weight loss are increased in CVID, as is liver disease (with granulomatous infiltration) and hepatitis. Poor growth rates can be seen in children. Immune dysregulation can result in enlargement of lymphoid structures, including splenomegaly, lymphadenopathy, and GI nodular lymphoid tissue. Risk for malignancy, especially lymphoma and gastric carcinoma, is significantly increased compared with the general population. The risk for autoimmune disorders, including immune thrombocytopenic purpura (ITP) and AIHA, is also significantly increased.

Odnoletkova I, Kindle G, Quinti I, et al. The burden of common variable immunodeficiency disorders: a retrospective analysis of the European Society for Immunodeficiency (ESID) registry data. *Orphanet J Rare Dis.* 2018;13(1):201.

Gathmann B, Mahlaoui N, Gerard L, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol.* 2014;134(1):116–126.

107. Why is the diagnosis of CVID commonly delayed?

Diagnostic delay, typically on the order of years, occurs for a number of reasons. Symptom onset often begins after a period of normal health. CVID is rarely diagnosed before 4 years of age, as hypogammaglobulinemia can represent a simple delay in the maturation of B cells (particularly before 2 years of age). Symptom presentations can be nonspecific and overlap with common pediatric disorders. There may be insufficient awareness of the condition itself. Studies of the age at diagnosis have loosely revealed two peaks, between 6 and 10 years of age (early-onset disease) and in young adulthood between 26 and 40 years (late-onset disease). In a study of 2212 patients, early-onset disease ($<$10 years) occurred in only one-third of cases, with average delays of diagnosis between 4 and 5 years.

Gathmann B, Mahlaoui N, Gerard L, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol.* 2014;134(1):116–126.

Urschel S, Kayikci L, Wintergerst U, et al. Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. *J Pediatr.* 2009;154(6):888–894.

108. What are secondary (or acquired) causes of decreased serum Igs?

Various conditions can cause Ig levels to fall below normal through multiple mechanisms, including hypercatabolism, accelerated protein loss, or inhibition of production.

- **Infection:** primarily viral (EBV, CMV, parvovirus B19)
- **Malignancy:** chronic lymphocytic leukemia, multiple myeloma
- **Medications:** corticosteroids, sulfasalazine, penicillamine, antiepileptics (phenytoin, carbamazepine, lamotrigine, valproic acid), various chemotherapeutic agents, rituximab, gold therapy (for rheumatoid arthritis)
- **Protein-losing enteropathy:** intestinal lymphangiectasia, Crohn disease
- **Renal protein loss:** nephrotic syndrome, SLE
- **Trauma:** burns

Jaffe EF, Lejtenyi MC, Noya FJ, et al. Secondary hypogammaglobulinemia. *Immunol Allergy Clin North Am.* 2001;21(1):141–163.

109. In an infant with panhypogammaglobulinemia, how can the quantitation of B and T lymphocytes in peripheral blood help distinguish the diagnostic possibilities?

- Normal numbers of T lymphocytes, no detectable B lymphocytes: X-linked agammaglobulinemia (Bruton disease)
- Normal numbers of T and B lymphocytes: Transient hypogammaglobulinemia of infancy, CVID
- Decreased numbers of T lymphocytes, normal or decreased numbers of B lymphocytes: SCID
- Decreased CD4 lymphocytes: HIV infection

KEY POINTS: WARNING SIGNS OF IMMUNODEFICIENCY

1. Four or more new ear infections within 1 year
2. Two or more serious sinus infections within 1 year
3. Two or more months on antibiotics with little effect
4. Two or more severe pneumonia infections within 1 year
5. Failure of an infant to gain weight and grow normally
6. Recurrent deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infection on skin after 1 year of age
8. Need for intravenous antibiotics to clear infections
9. Two or more deep-seated infections such as meningitis, osteomyelitis, cellulitis, or sepsis
10. A family history of primary immunodeficiency

110. What is the underlying disorder in an 8-year-old girl with atypical eczema, pneumatoceles, and bouts of severe furunculosis?

Hyper-IgE syndrome is the most likely diagnosis. This disease is clinically characterized by the following:

- Recurrent infections (almost invariably caused by *Staphylococcus aureus*) of the skin, lungs (causing frequently persistent pneumatoceles), ears, sinuses, eyes, joints, and viscera
- Atypical eczema with lichenified skin
- Coarse facial features, especially the nose
- Osteopenia of unknown cause
- Delayed tooth exfoliation (i.e., prolonged retention of primary teeth)

The laboratory evaluation of hyper-IgE syndrome reveals massively elevated IgE levels associated with IgG subclass and specific antibody deficiencies, variable dysfunctions of neutrophils, and an imbalance of cytokine production as a result of a Th2 predominance (IL-4, IL-5).

Farmand S, Sundin M. Hyper-IgE syndromes: recent advances in pathogenesis, diagnostics and clinical care. *Curr Opin Hematol*. 2015;22(1):12–22.

Heimall J, Freeman A, Holland SM. Pathogenesis of hyper IgE syndrome. *Clin Rev Allergy Immunol.* 2010;38(1):32–38.

111. What are the proven indications for intravenous immunoglobulin (IVIG) therapy?

More than 75% of IVIG used in the United States is for the treatment of autoimmune or inflammatory conditions. Dosing in those conditions is typically four to five times greater than replacement therapy in immunodeficiency disease. Indications for IVIG are:

- Primary immunodeficiency disease
- Chronic lymphocytic leukemia
- Pediatric HIV disease
- Kawasaki disease
- Allogeneic bone marrow transplantation
- AIHA
- ITP
- Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculopathy)
- Chronic inflammatory demyelinating polyradiculoneuropathy
- CMV-induced pneumonia in solid organ transplant recipients
- Various dermatologic conditions (including toxic epidermal necrolysis)

Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Engl J Med.* 2012;367(21):2015–2025.

112. What are the pharmacologic characteristics of IVIG?

After the infusion, 100% of the IgG stays in the intravascular compartment. Over the course of the next 3 to 4 days, IgG equilibrates with the extracellular space, with 85% of the infused IgG still situated in the circulation. By the end of the first week, half of the IgG given has left the circulation, and by 4 weeks after the infusion, the serum levels have returned to baseline. However, these data apply to healthy individuals with a regular catabolism, and they have to be adjusted for both patients with a higher metabolic rate and for individuals transfused with increased IgG concentrations.

113. What are the adverse reactions to IVIG?

The common infusion rate–related adverse events are chills, headache, fatigue and malaise, nausea and vomiting, myalgia, arthralgia, and back pain. Less frequent reactions are abdominal and chest pains, tachycardia, dyspnea, and changes in blood pressure. Serious but rare side effects include aseptic meningitis, thrombosis, DIC, renal and pulmonary insufficiency, and anaphylaxis in complete IgA-deficient individuals due to IgE antibodies specific for IgA. Subcutaneous therapy can reduce the occurrence of systemic adverse events in selected patients.

114. You are asked to evaluate a 9-month-old male with eczema and recurrent respiratory infections who was found to be thrombocytopenic. What diagnosis must be considered?

Wiskott-Aldrich syndrome is an X-linked disease characterized by the classic triad of *eczema, thrombocytopenia (with small platelet size)*, and *combined B-cell and T-cell immunodeficiency*. It is caused by mutations in the *WAS* gene (found on the short arm of the X chromosome). The initial manifestations are often present at birth and consist of petechiae, bruises, and bloody diarrhea as a result of thrombocytopenia. The eczema is similar in presentation to classical atopic eczema (antecubital and popliteal fossa). Infections are common and include (in decreasing frequency) otitis media, pneumonia, sinusitis, sepsis, and meningitis. The severity of immunodeficiency may vary but usually affects both T-cell and B-cell functions. It is important to note that this immunodeficiency is progressive and associated with a high risk for developing cancer. A teenager with this condition has a 10% to 20% statistical risk for developing a lymphoid neoplasm. Of note, only about one-third of patients with Wiskott-Aldrich syndrome present with the classic triad.

Massaad MJ, Ramesh N, Geha RS. Wiskott-Aldrich syndrome: a comprehensive review. *Ann NY Acad Sci.* 2013;1285:26–43.

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115. What is the likely diagnosis of a patient presenting with a progressive ataxia, conjunctival abnormalities, and recurrent bacterial sinopulmonary infections?

Ataxia-telangiectasia. In patients with ataxia-telangiectasia, primarily progressive cerebellar ataxia develops during infancy and is typically associated with other neurologic symptoms (e.g., the loss or decrease of deep tendon reflexes, choreoathetosis, apraxia of eye movements). The signs of telangiectasia occur usually after the onset of ataxia, generally between 2 and 8 years of age. The telangiectasias are primarily at the bulbar conjunctivae (Fig. 9.9). Recurrent infections (as a consequence of a humoral and cellular immunodeficiency) are observed in 80% of patients with ataxia-telangiectasia and are typically localized to the middle ear and the upper airways.

Rothblum-Oviatt C, Wright J, Lefton-Greif MA, et al. Ataxia telangiectasia: a review. *Orphanet J Rare Dis.* 2016;11(1):159.

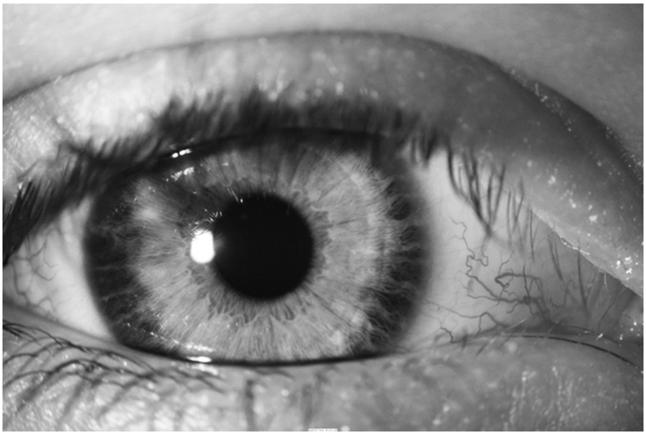

Fig. 9.9 Telangiectasia of the conjunctiva. (From Orth KAHM, Leung H, Andrews I, Sachdev R. Ataxia telangiectasia in a three-year-old girl. *Pediatr Neurol.* 2014;50:279.)

116. What disease did the “bubble boy” have?

Adenosine deaminase (ADA) deficiency. In this form of SCID, the lack of ADA results in abnormalities of B- and T-cell function and increased susceptibility to infection. The term refers to a patient from Texas (David Vetter) who received significant media attention during his shortened life span (1971–1984) because of his requirement for a complex containment system. The “bubble” served as a means of minimizing contagion but also promoted social isolation. Although bone marrow transplantation has been curative as a treatment for this condition, ADA deficiency is the first disease to be treated by gene therapy (i.e., insertion of functional ADA genes into the patient’s autologous cells and followed by infusion).

Aiuti A, Cattaneo F, Galimberti S, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. *N Engl J Med.* 2009;360(5):447–458.

117. What is the molecular defect of CGD?

CGD is characterized by a profound defect in the **oxygen metabolic burst** in myeloid cells following the phagocytosis of microbes. The molecular mechanisms responsible for this disease are heterogenous because any defect of the four subunits that constitute the NADPH-oxidase can cause CGD. As a consequence, superoxide, oxygen radicals, and peroxide production are lacking, and patients with CGD cannot kill catalase-positive pathogenic bacteria and fungi (e.g., *Staphylococcus aureus; Nocardia, Serratia,* and *Aspergillus* species).

Arnold DE, Heimall J. A review of chronic granulomatous disease. *Adv Ther.* 2017;34(12):2543–2557.

118. Which laboratory tests are used for the diagnosis of CGD?

Patients suspected to have CGD can be diagnosed as a result of their failure to generate reactive oxygen species during the respiratory burst or, alternatively, as a result of their inability to kill catalase-positive bacteria in vitro with their phagocytes. The screening tests for the production of superoxide are the slide nitroblue tetrazolium (NBT) reduction test and the flow cytometric 2′,7′-dichlorofluorescein test.

119. What types of infections are commonly seen in children with CGD?

Superficial staphylococcal skin infections, particularly around the nose, eyes, and anus, are common. Severe adenitis, recurrent pneumonia, indolent osteomyelitis, and chronic diarrhea are frequent. A male child with a liver abscess should be considered to have CGD until it is proved otherwise.

120. Which disorder has to be considered in a newborn patient with delayed separation of the umbilical cord?

Separation of the umbilical cord occurs normally on average by 10 days of life, with a range of 3 to 45 days. Delayed separation can occur in patients with **leukocyte adhesion deficiency type 1** (LAD1), who suffer from a profound impairment of leukocyte mobilization into extravascular sites. The hallmark of this disorder is the complete absence of neutrophils at the site of infection and inflammation (e.g., wound healing); peripheral blood neutrophil counts are greatly increased.

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van de Vijver E, van den Berg TK, Kuijpers TW. Leukocyte adhesion deficiencies. *Hematol Oncol Clin North Am.* 2013;27(1):101–116.

121. Which potential life-threatening disorder of the complement system is associated with nonpruritic swelling and occasional recurrent abdominal pain?

Hereditary C1-esterase inhibitor deficiency. Angioedema of any part of the body—including the airway and the intestine—can occur as a consequence of failure to inactivate the complement and kinin systems. The condition has also been called *hereditary angioneurotic edema*. Infections, oral contraceptives, pregnancy, minor trauma, stress, and other variables have been noted to precipitate this autosomal dominant disease. Drugs used for treatment and prevention of acute flares of this disorder include androgens (particularly danazol), plasma-derived C1-esterase inhibitor concentrates, and recombinant C1-esterase inhibitor concentrates. Diagnosis is confirmed by direct assay of the inhibitor level. Clinical presentations include the following:

- *Recurrent facial and extremity swelling:* Acute, circumscribed edema that is not painful, red, or pruritic, thereby clearly distinguished from urticaria; usually self-resolves in 72 hours
- *Abdominal pain:* Recurrent and often severe, colicky pain as a result of interstitial wall edema with vomiting and/or diarrhea; may be misdiagnosed as an acute abdomen
- *Hoarseness, stridor:* A true emergency because death by asphyxiation may occur as a result of laryngeal edema; epinephrine, hydrocortisone, and antihistamines are often of only limited benefit; and tracheostomy is needed if there is progression of symptoms

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Bork K. An evidence-based therapeutic approach to hereditary and acquired angioedema. *Curr Opin Allergy Clin Immunol.* 2014;14(4):354–362.
Zuraw BL. Hereditary angioedema. *N Engl J Med.* 2008;359(10):1027–1036.

IMMUNOLOGY LABORATORY

122. Which are the initial screening tests for a suspected immunodeficiency?

The basic screening tests should include **CBC** (including hemoglobin, morphology, and absolute cellularity); **quantification of Ig levels** (IgM, IgG, IgE, and IgA); **antibody responses to previous antigen exposures** (e.g., vaccines, pathogen-defined infections); **determination of isohemagglutinin titers**; assessment of the classic complement pathway by determining the **CH$_{50}$**; and **workup of infections**, including determination of C-reactive protein, blood cultures, and appropriate radiography. The choice of the laboratory tests is generally dependent on the clinical findings and the immunodeficiency suspected. Results should always be compared with age-matched controls.

123. Which laboratory tests allow for a broad evaluation of the humoral immune system?

- **Serum Ig levels, quantitative:** IgM, IgG, IgA, and IgE. A combined IgG, IgA, and IgM level of $<$400 mg/dL suggests Ig deficiency; $>$5000 IU/mL for IgE suggests hyper-IgE syndrome.
- **IgG subclasses:** These Igs should generally be measured primarily in patients $>$6 years old, in certain circumstances (e.g., in patients with selective IgA deficiency and normal to low IgG concentrations but demonstrated functional antibody deficiency), and in patients with recurrent sinopulmonary infections.
    - Specific antibody titers: In response to documented infections and vaccinations
    - Isohemagglutinin titer (anti-A, anti-B): 1:4 or less after the age of 1 year suggests specific IgM deficiency
    - Tetanus, diphtheria (IgG1)
    - Pneumococcal polysaccharide antigens (IgG2)
    - Viral respiratory agents (IgG3)
- **Determination of B-cell numbers:** In the peripheral blood with the use of flow cytometry (CD19, CD20)
- **B-cell proliferation and Ig production:** With the use of in vitro assays

124. Which diagnostic tests allow for the specific evaluation of T-cell functions?

- **Total lymphocyte count:** Although most T-cell immunodeficiencies are not associated with a decreased lymphocyte count, a total count of $<$1500/mm^3 suggests a deficiency.

- **T-cell subpopulations:** Total T cells with $<60\%$ mononuclear cells, helper (CD4) cells $<200/\mu L$, or CD4/CD8 <1.0 suggest T-cell deficiency.
- **Delayed-type hypersensitivity skin testing**
- **Proliferative responses** to mitogens, antigens, and allogeneic cells
- **Acquisition of activation markers** on T cells (using flow cytometry)
- **Cytotoxic assay**
- **Cytokine synthesis**
- **Adenosine deaminase** and **purine nucleoside phosphorylase** determination in RBCs
- **Molecular biologic studies** (including karyotyping and fluorescent in situ hybridizations)
- **Histology** of thymic and lymph-node biopsies

125. What is the value of skin testing for the diagnosis of T-cell deficiencies?

Skin tests for the assessment of delayed-type hypersensitivity are difficult to evaluate. A positive test is useful for eliminating the diagnosis of severe T-cell deficiency, whereas a negative test may reflect a T-cell defect, or it may result from the lack of an anamnestic response to the antigens used. Seventy-five percent of normal children between the ages of 12 and 36 months will respond to *Candida* skin testing at 1:10 dilution, and, by 18 months, about 90% of normal children will respond to one of a panel of recall antigens (tetanus toxoid, trichophyton, and *Candida*); the younger the child, the less likely the reactivity. The cell-mediated reaction may be obscured by a humoral (Arthus) reaction as a result of previous priming.

126. What is the importance of the CD4/CD8 ratio?

The *CD4/CD8 ratio* is an index of helper to suppressor and cytotoxic cells and may be significantly altered in patients with a variety of immunodeficiencies. In normal individuals, the ratio ranges from 1.4:1.0 to 1.8:1.0. In patients with viral infections (particularly HIV), the ratio can be reduced; in patients with bacterial infections, it can be increased.

127. Which laboratory tests appropriately evaluate the phagocytic system?

- **Absolute granulocyte count**
- **Antineutrophil antibodies** (however, antineutrophil antibodies are found in only one-half of the cases of autoimmune neutropenia)
- **Bone marrow biopsy** (to differentiate increased consumption from decreased production)
- **Specific in vitro and in vivo assays:**
  - *Determination of chemotaxis*: in vivo (skin wounds) or in vitro (Boyden chambers): Measurements are not routinely used for diagnostic purposes
  - *Quantification of neutrophil adherence*: Measurement of cell surface expression of leukocyte function antigen-1 (CD11/CD18) by flow cytometry; adherence to inert surfaces such as nylon, wool, or plastic
  - *Determination of the respiratory burst*: (1) NBT measures the ability of phagocytic cells to ingest and reduce a yellow dye to an intercellular blue crystal; (2) Dihydrorhodamine (DHR)—in activated granulocytes reactive oxygen intermediates reduce DHR 123 to rhodamine 123, which results in an increase in fluorescence that can be quantified by flow cytometry
  - *Enzyme assays* (myeloperoxidase, G6PD, glutathione peroxidase, NADPH-oxidase)
  - *Test treatment with GCSF*. Autoimmune forms of neutropenia in small children respond to minor doses (1 mcg/kg) within a couple of days, whereas congenital forms require larger doses with responses after 2 to 3 weeks of treatment
  - *Mutational analysis*

128. How is the classic complement cascade evaluated?

The primary screening test is the **CH_{50}**. This test assesses the ability of an individual's serum (in varying dilutions) to lyse sheep RBCs after those cells are sensitized with rabbit IgM anti-sheep antibody. The CH_{50} is an arbitrary unit that indicates the quantity of complement necessary for 50% lysis of the RBCs in a standardized setting. Test results are usually expressed as a derived reciprocal of the test dilution needed for 50% lysis. The test is relatively insensitive because major reductions in individual complement components are necessary before the CH_{50} is altered. Therefore determination **C3** and **C4 levels** is often included in the initial screening of a child with a suspected complement deficiency.

IRON-DEFICIENCY ANEMIA

129. What is the world's most common single-nutrient deficiency?

According to the World Health Organization, it is **iron**. It is estimated that 2 billion people, or over 30% of the world's population, are anemic, many due to iron deficiency. In developing countries, about 40% of preschool children are estimated to be anemic.

World Health Organization. www.who.int/nutrition. Accessed July 7, 2019.

130. At what age do exclusively breastfed infants become at risk for iron deficiency?

Healthy term infants who are exclusively breastfed are at risk for iron deficiency after they are **4 to 6 months old**. The American Academy of Pediatrics (AAP) Committee on Nutrition has recommended that exclusively breastfed infants be supplemented with iron (1 mg/kg per day) starting at 4 months of age and continued until appropriate iron-containing complementary foods have been introduced. The age of risk for exclusively breastfed premature infants can be more complicated, particularly for the smaller and sicker infants. The lower iron stores of premature infants are more rapidly depleted compared with term babies. The AAP Committee on Nutrition recommends that all preterm breastfed infants receive an iron supplement (2 mg/kg per day) by 1 month of age and that it be continued until sufficient iron-containing foods or formula is being consumed.

Hernell O, Fewtrell MS, Georgieff MK, et al. Summary of current recommendations on iron provision and monitoring of iron status for breastfed and formula-fed infants in resource-rich and resource-constrained countries. *J Pediatr.* 2015;167(4 Suppl):S40–S47.

Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics.* 2010;126(5):1040–1050.

131. Why are infants who begin consuming cow milk at an early age susceptible to iron-deficiency anemia?

Lower bioavailability. Although breast milk and cow milk contain about the same amount of iron (0.5 to 1.0 mg/L), iron is absorbed at 50% efficiency from breast milk but at only 10% from cow milk. In addition, cow milk may cause **microscopic GI bleeding** in younger infants as a result of mucosal injury, possibly from sensitivity to bovine albumin. In older infants, cow milk may interfere with iron absorption from other sources.

Throsdottir AV, Ramel A, Tomassson H, Thorsdottir I. Iron-status of one-year-olds and association with breast milk, cow's milk or formula in late infancy. *Eur J Nutr.* 2013;52(6): 1661–1668.

132. As iron becomes depleted from the body, what is the progression at which laboratory tests change?

As shown in Fig. 9.10, the left end of the line for each test indicates the point at which the result deviates from its baseline. In general, the depletion of marrow, liver, and spleen reserves (as represented by ferritin) occurs first. This is followed by a decrease in transport iron (as represented by transferrin saturation) and finally a fall in hemoglobin and MCV. The figure illustrates that the absence of anemia does not exclude the possibility of iron deficiency and that iron depletion is relatively advanced before anemia develops. Tests of soluble transferrin receptor have become of interest in patients with iron-deficiency anemia, especially in inflammatory conditions where ferritin may be elevated.

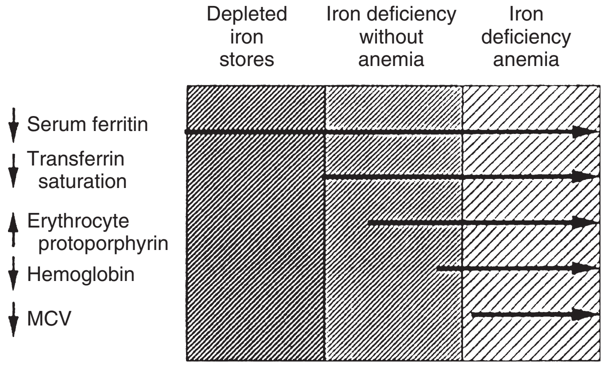

Fig. 9.10 Progression of laboratory test changes with iron depletion. *MCV,* Mean corpuscular volume. (From Dallman PR, Yip R, Oski FA. Iron deficiency and related nutritional anemias. In Nathan DG, Oski FA, eds. *Nathan and Oski's Hematology of Infancy and Childhood.* 4th ed. Philadelphia, PA: W.B. Saunders; 1993:427.)

133. How might the reticulocyte hemoglobin content be helpful for the diagnosis of iron deficiency?

Because the reticulocyte is the most recently produced RBC in circulation, the earliest sign of iron deficiency may be a fall in the concentration of hemoglobin in reticulocytes. This number can be calculated from automated counting equipment and may be a reliable and inexpensive alternative to ferritin. Studies have indicated that patients with a concentration of ≥30 pg per cell have virtually no chance of iron deficiency.

Piva E, Brugnara C, Spolaore F, Plebani M. Clinical utility of reticulocyte parameters. *Clin Lab Med.* 2015;35(1):133–163.

Brugnara C, Zurakowski D, DiCanzio J, et al. Reticulocyte hemoglobin content to diagnose iron deficiency in children. *JAMA.* 1999;281(23):2225–2230.

134. Why are tests for iron stores more difficult to interpret during acute inflammatory states?

The *ferritin* level, which is used to monitor body iron stores, is exquisitely sensitive to inflammation, increasing even with mild upper respiratory infections. Elevations of ferritin may persist for some time. By contrast, *serum iron, transferrin level,* and *percent transferrin saturation* may decrease with infection or inflammation. *Free erythrocyte protoporphyrin* should not be affected by acute inflammation, but may increase in chronic inflammatory states.

Suchdev PS, Williams AM, Mei Z, et al. Assessment of iron status in settings of inflammation: challenges and potential approaches. *Am J Clin Nutr.* 2017;106(Suppl 6):1626S–1633S.

135. What is the role of hepcidin in iron metabolism?

Hepcidin is part of the system of iron regulatory proteins. The iron regulatory system controls intestinal iron absorption, blood transport, tissue deposition, and mobilization of stores for utilization. Hepcidin is synthesized in the liver and participates in the orchestration of uptake and utilization.

Muckenthaler MJ, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. *Cell.* 2017;168(3):344–361.

136. What are the common causes of microcytic anemia in children?

- *More common:* Iron deficiency (from nutritional insufficiency and/or blood loss), thalassemia (α- or β-; major, minor, or trait)
- *Less common:* Lead toxicity, hemoglobinopathy (with or without thalassemia), chronic inflammation, copper deficiency, sideroblastic anemia

137. How is the RDW useful for distinguishing causes of microcytic anemia?

The *RDW* is a quantification of anisocytosis (variation in RBC size). In children, normal values range from about 11.5% to 14.5% but can vary among instruments. Statistically, it is the coefficient of variation of RBC volume distribution. When elevated in a patient with microcytosis, it suggests that iron deficiency is a more likely cause of anemia than the thalassemia trait. Children with the thalassemia trait tend to have values that overlap with normal RDW values. The combination of an RDW above the normal range with a free erythrocyte protoporphyrin level of >35 μg/dL is more sensitive and specific for iron-deficiency anemia.

138. What is the Mentzer index?

MCV / RBC (mean corpuscular volume / red blood cell count). This is one of the formulas used to distinguish the hypochromic, microcytic anemias of the thalassemia trait from iron deficiency. As a general rule, iron deficiency causes alterations in RBCs that tend to be variable, whereas thalassemia generally results in more uniformly smaller cells and the RBC number is preserved. In patients with the β-thalassemia trait, the Mentzer index is usually <13; in patients with iron deficiency, it is usually >13.

139. In a child with suspected iron-deficiency anemia, is a therapeutic trial with iron an acceptable diagnostic approach?

Yes. If an infant or child is otherwise well, a therapeutic trial of 4 to 6 mg/kg per day of elemental iron can substitute for additional diagnostic testing (e.g., ferritin, transferrin saturation, free erythrocyte protoporphyrin), because dietary iron deficiency is the most likely cause of microcytic anemia. If the child is iron deficient, is compliant with therapy, and there is not ongoing undetected blood loss, the hemoglobin should rise by >1 g/dL in about 2 weeks. If the hemoglobin does rise, therapy should be continued for an additional 2 months to replenish iron stores.

140. After iron therapy is initiated, how early can a response be detected?

- *2 to 5 days:* Increase in reticulocyte count
- *7 to 10 days:* Increase in hemoglobin level

For patients with mild iron-deficiency anemia, the hemoglobin level should be checked after several weeks of therapy. For patients with more severe anemia, it may be useful to check the hemoglobin and reticulocyte levels after several days to make certain that the hemoglobin has not declined to dangerous levels and that the reticulocyte response is beginning.

141. What foods affect the bioavailability of nonheme iron?

It is *decreased by* phosphates, tannates, polyphenols, and oxalates found in cereal, eggs, milk, cheese, tea, and complex carbohydrates. It is *increased by* fructose; citrate; and, especially, ascorbic acid found in red kidney beans, cauliflower, and bananas. In children with iron deficiency, the administration of replacement iron with a vitamin C–fortified fruit juice 30 minutes before a meal makes physiologic sense.

142. What are the options for the use of parenteral iron therapy?

When oral iron therapy has failed or cannot be used, there are several formulations of iron for intravenous use with generally good tolerance. These include formulations such as iron sucrose, sodium ferric gluconate, and ferric carboxymaltose. Usually repletion of iron stores requires multiple treatments over time; however, novel parenteral iron supplements (iron isomaltoside) may only require single-dose administration. Care must be exercised in administration to avoid untoward side effects. Monitoring is required to ensure that anemia is reversed and that iron stores are restored.

Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency. *Lancet.* 2016;27;387(10021):907–916.

143. What are the differences between pica, geophagia, and pagophagia?

All are clinical markers that suggest the diagnosis of iron deficiency. *Pica* is a more general term that indicates a hunger for material that is not normally consumed as food. *Geophagia* refers to the consumption of dirt or clay, and *pagophagia* refers to the excessive consumption of ice. These are distinguished from *cissa*, which is the physiologic craving during pregnancy for unusual food items or combinations.

144. What is the derivation of the term *pica*?

The condition comes from the Latin term for the magpie, *Pica hudsonia.* This bird is believed to eat almost anything; hence, the term *pica* for the tendency to eat nonnutritional substances.

Borgna-Pignatti C, Marsella M. Iron deficiency in infancy and childhood. *Pediatr Ann.* 2008;37(5):332–333.

145. What is the relationship between iron deficiency and neurocognitive development in infants and toddlers?

Multiple studies have shown an association between iron deficiency in infants between 9 and 24 months old and lower motor and cognitive scores and increased behavioral problems compared with nonanemic controls. Some longer-term studies suggest that the developmental impairments may be long lasting. Debate remains about whether this relationship is causal and, if so, whether the early detection and correction of anemia lead to a reversal of the problems. Iron supplementation has not been shown to result in short-term improvements.

Wang B, Zhan S, Gong T, Lee L. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anemia. *Cochrane Database Syst Rev.* 2013;6:CD001444.

Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics.* 2010;126(5):1040–1050.

146. What are the risk factors for iron deficiency or iron-deficiency anemia in a 1-year-old?

- Low socioeconomic status (especially children of Mexican American descent)
- Exposure to lead
- History of prematurity or low birth weight
- Exclusive breastfeeding beyond 4 months of age without supplemental iron
- Introduction of whole milk before 1 year of age
- Feeding problems
- Poor growth
- Inadequate nutrition (particularly seen in infants with special care needs)

147. Why are iron-deficient children at increased risk for lead poisoning?

- Pica associated with iron deficiency increases the likelihood of ingestion of lead-contaminated items.
- GI absorption of lead may be increased in patients who consume less iron-containing nutrients.

Watson WS, Morrison J, Bethel MI, et al. Food iron and lead absorption in humans. *Am J Clin Nutr.* 1986;44(2):248–256.

148. How and when should younger children be screened for iron deficiency?

This is **controversial**. AAP recommendations, which previously had advised selective screening only, began in 2010 to advocate universal screening at approximately 12 months of age with a hemoglobin measurement and an assessment of risk factors for iron deficiency/iron-deficiency anemia. Critics have argued that this type of screening process does not identify early enough those with iron problems, including by definition those with iron deficiency alone before the development of anemia. Additionally, critics contend that although hematologic values may improve with supplementation, evidence on longer-term clinical outcomes is lacking. Other screening tests that have been suggested as better biomarkers of iron status include reticulocyte hemoglobin concentration, transferrin saturation, serum transferrin receptor 1 (TfR1) concentration, and zinc protoporphyrin. Zinc protoporphyrin is an RBC-specific intermediary metabolite required for the biosynthesis of hemoglobin.

McDonagh MS, Blazina I, Dana T, et al. Screening and routine supplementation for iron deficiency anemia: a systematic review. *Pediatrics.* 2015;135(4):723–733.

Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics.* 2010;126(5):1040–1050.

KEY POINTS: IRON-DEFICIENCY ANEMIA

1. The introduction of whole cow milk before the age of 1 year increases risk as a result of occult GI bleeding.
2. RDW is increased because deficiency results in uneven RBC size (anisocytosis).
3. Low levels of ferritin indicate diminished tissue iron stores.
4. This condition may impair cognitive development in infants.
5. Absence of anemia does not exclude the possibility of iron deficiency. Iron depletion is relatively advanced before anemia occurs.

MEGALOBLASTIC ANEMIA

149. What is megaloblastic anemia?

Megaloblastic anemia is a macrocytic anemia that is characterized by large RBC precursors (megaloblasts) in the bone marrow and that is usually caused by nutritional deficiencies of either folic acid (folate) or vitamin B_{12} (cobalamin).

150. Is megaloblastic anemia the most common cause of macrocytic anemia?

No. Macrocytic anemia can be found in conditions associated with a high reticulocyte count (e.g., hemolytic anemia, hemorrhage), bone marrow failure (e.g., Fanconi anemia, aplastic anemia, Diamond-Blackfan anemia), liver disease, Down syndrome, and hypothyroidism.

151. What findings on a CBC are suggestive of megaloblastic anemia?

- *RBCs:* elevated MCH and mean cell volume (often 106 fL or more), with normal MCHC; marked variability in cell size (anisocytosis) and shape (poikilocytosis)
- *Neutrophils:* hypersegmentation ($>5\%$ of neutrophils with five lobes or a single neutrophil with six lobes)
- *Platelets:* usually normal; thrombocytopenia in more severe anemia

152. What are the causes of vitamin B_{12} (cobalamin) deficiency in children?

Decreased intake

- May occur in vegetarians who consume no animal products
- Seen in exclusively breastfed infants of B_{12}-deficient mothers
- General malnutrition

Decreased absorption

- Ileal mucosal abnormalities (e.g., Crohn disease)
- Surgical resection of terminal ileum (e.g., infant with history of surgical necrotizing enterocolitis [NEC])
- Competition for cobalamin in bacterial overgrowth syndromes or infection with the fish tapeworm *Diphyllobothrium latum*
- Congenital abnormalities of the receptor for vitamin B_{12}–intrinsic factor complex
- Gastric mucosal defects that interfere with the secretion of intrinsic factor

153. What are the best dietary sources of folate and B_{12}?

- *Folate*: Folate-rich foods include liver, kidney, and yeast. Good sources also include green vegetables (particularly spinach) and nuts. Moderate sources include fruits, bread, cereals, fish, eggs, and cheese. Pasteurization or boiling destroys folate.
- *Vitamin B_{12}*: Humans do not manufacture B_{12}; bacteria and fungi do. Animals require it, whereas plants do not. Consequently, our major dietary source of vitamin B_{12} is the consumption of animal tissue, milk, or eggs. Fish and shellfish, which live on bacterial diets, are also a good dietary source. Of note is that B_{12} is required for normal folate metabolism.

154. What is pernicious anemia?

Pernicious anemia is a megaloblastic anemia that is caused by a **lack of intrinsic factor**. Intrinsic factor is a glycoprotein that is released from the gastric parietal cells and binds to vitamin B_{12} to form a complex that is ultimately absorbed in the terminal ileum.

155. A 10-month-old child who was exclusively fed goat milk is likely to develop what type of anemia?

Megaloblastic anemia as a result of folic acid deficiency. Goat milk contains very little folic acid compared with cow milk. Infants who are consuming large amounts of goat milk— especially if they are not receiving significant supplemental solid foods—are susceptible to this type of anemia. In addition, the diagnosis can be complicated by the higher risk for coexistent iron-deficiency anemia in this age group.

PLATELET DISORDERS

156. How can a platelet count be estimated from a peripheral smear?

As a rule, each platelet that is visible on a high-power microscopic field (100 × objective) represents 15,000 to 20,000 platelets/mm^3. If platelet clumps are observed, the count is usually $>100{,}000$/mm^3.

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157. What are the main pathophysiologic processes that can result in thrombocytopenia?

- Peripheral destruction
- Consumptive coagulopathy
- Splenic sequestration
- Bone marrow failure

158. A previously healthy 3-year-old child develops mucosal petechiae, multiple ecchymoses, and a platelet count of 20,000/mm^3 2 weeks after a bout of chickenpox. What is the most likely diagnosis?

Acute ITP. ITP is one of the most common bleeding disorders of childhood, and the presentation of symptoms occurs after infection in about 50% of cases.

D'Orazio JA, Neely J, Farhoudi N. ITP in children: pathophysiology and current treatment approaches. *J Pediatr Hematol Oncol.* 2013; 35(1):1–13.

159. What microscopic features would suggest a diagnosis other than ITP in a patient with a platelet count of 20,000/mm^3?

- **Platelet clumps** (in vitro phenomenon caused by ethylenediaminetetraacetic acid [EDTA] that results in artifactually low platelet counts)
- **Leukemic blasts**
- **RBC fragments** (suggest a microangiopathic etiology such as hemolytic-uremic syndrome or Kasabach-Merritt syndrome)
- **Large platelets** (seen in inherited platelet disorders such as Bernard-Soulier syndrome, MYH9 syndromes, DiGeorge syndrome)
- **Atypical lymphocytes** (thrombocytopenia rarely occurs as part of infectious mononucleosis)
- **Uniformly small platelets** (a feature of Wiskott-Aldrich syndrome)

Thachil J, Hall GW. Is this immune thrombocytopenic purpura? *Arch Dis Child.* 2008;93(1):76–81.
Drachman JG. Inherited thrombocytopenia: when a low platelet count does not mean ITP. *Blood.* 2004;103(2):390–398.

160. What is the natural history of acute childhood ITP?

With or without medical treatment, 50% to 60% of patients with acute ITP will have normal platelet counts within 1 to 3 months of diagnosis, and 75% are well after 6 months. By 1 year, only 10% of children with ITP remain thrombocytopenic, and some of the children with chronic ITP still improve as far out as 5 to 10 years after diagnosis. About 5% of patients have recurrent ITP. Because of this predominantly benign natural course of ITP, careful consideration is necessary before instituting treatment that is hazardous or irreversible.

161. In a toddler with suspected ITP, what is the significance of a palpable spleen on examination?

Although patients with ITP may rarely have a palpable spleen tip, the presence of splenomegaly in a patient with thrombocytopenia warrants more aggressive evaluation for an associated problem (e.g., collagen-vascular disease, hypersplenism, leukemia, glycogen storage disorder).

162. In patients with suspected ITP, should a bone marrow evaluation be done?

Guidelines suggest that with classic ITP, there is no need for a bone marrow examination even in patients who have failed IVIG and may require steroids. However, if a patient has features that are potentially consistent with an alternative diagnosis, such as other cytopenias, organomegaly, or an atypical history and physical examination, a bone marrow evaluation should be considered.

Neunert CE, Cooper N. Evidence-based management of immune thrombocytopenia: ASH guideline update. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):568–575.
Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood.* 2011;117:4190–4207.

163. When should medical treatment be given for acute ITP without active bleeding?

Because the long-term prognosis of ITP does not appear to be influenced by medical treatment, the management of a newly diagnosed child with ITP and no serious bleeding is observation and specific instructions for thrombocytopenic precautions. Historically, the concern at very low platelet counts ($<$10,000/mm^3) was the risk for intracranial hemorrhage, which was rare ($<$1% of affected patients), but had mortality rates that ranged from 30% to 50%. However, current data suggest that the risks of up-front therapy in a child with minimal or no bleeding outweigh the potential benefits. Up-front therapy should be considered for those patients who may fail to follow thrombocytopenic precautions (such as active toddlers) or those who already have significant bleeding.

Neunert CE, Cooper N. Evidence-based management of immune thrombocytopenia: ASH guideline update. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):568–575.

Cuker A, Cines DB, Neunert CE. Controversies in the treatment of immune thrombocytopenia. *Curr Opin Hematol.* 2016;23(5):479–485.

Cooper N. A review of the management of childhood immune thrombocytopenia: how can we provide an evidence-based approach? *Br J Haematol.* 2014;165:756–767.

164. What are thrombocytopenic precautions in children?

The goal of thrombocytopenic precautions is to prevent significant trauma in children who may be at risk for bleeding as a result of their ITP. An easy rule of thumb for families is for the child to keep one foot on the ground at all times (no climbing, swinging, diving, etc.), as this limits the height of the fall a child could take.

165. How do treatments for acute ITP compare?

- **IVIG:** 0.8 to 1.0 g/kg per day raises the platelet count in approximately 85% of patients. The response usually occurs within 48 hours and persists for 3 to 4 weeks. Up to 75% of patients will have some degree of limited adverse reaction (e.g., nausea, vomiting, headaches, fever). IVIG is more expensive than steroids.
- **Corticosteroids:** Corticosteroids are similarly effective, but oral steroids take about twice as long (4 days) to raise the platelet count significantly. The steroid effect may be multifactorial because signs of hemorrhage tend to decrease before the increase in platelets occurs. This may include an improvement in microvascular endothelial stability. Side effects of long-term frequent steroid use are multiple.
- **Anti-D immunoglobulin:** Anti-D immunoglobulin (Ig with antibody Rh [D]) should be given intravenously to individuals with adequate hemoglobin levels, (Rh)D-positive RBCs, and intact splenic function. It is administered more quickly than IVIG, with a slightly smaller proportion of responders.
- **Splenectomy**: When done laparoscopically, splenectomy successfully restores the platelet count to safe ($>$50 k/μL) or normal ($>$150 k/μL) levels in 75% to 80% of patients who fail drug therapy. Preoperative immunization against encapsulated bacteria is necessary to minimize the risk for postsplenectomy sepsis; many also advocate oral antibiotic prophylaxis postoperatively.
- **Anti-CD20 (rituximab)**: In refractory severe cases, antibody therapy directed at B-lymphocyte CD20 has achieved some partial and complete responses that are sustained.

166. Which children with ITP are candidates for splenectomy?

Splenectomy improves the platelet count in up to 90% of patients. Because spontaneous remission is common in acute ITP, splenectomy is usually limited to bleeding that is life threatening or in chronic patients unresponsive to medical therapies. Patients with ITP lasting $>$1 year with continued bleeding, severe thrombocytopenia, or unacceptable restrictions may be reasonable candidates for splenectomy.

167. What other laboratory evaluations should be considered in a patient with persistent refractory thrombocytopenia?

- **Antinuclear antibody, double-stranded DNA, C3, C4, p-ANCA** (to rule out SLE and other collagen vascular diseases)
- **Quantitative Ig levels, pneumococcal titers** (to rule out common variable immune deficiency)
- **Bone marrow aspiration or biopsy** (to evaluate for possible myelodysplastic syndrome or marrow failure)
- **Viral studies** (including polymerase chain reaction for HIV, hepatitis C, EBV, CMV, parvovirus, and human herpesvirus 6 and 8)

Kalpatthi R, Bussel JB. Diagnosis, pathophysiology and management of children with refractory immune thrombocytopenic purpura. *Curr Opin Pediatr.* 2008;20(1):8–16.

168. Is there a role for stimulating platelet production in ITP therapy?

In chronic ITP, use of agonists of the thrombopoietin (TPO) receptor have shown efficacy in increasing platelet counts to safe levels. The effect lasts only during the time period in which the drug is being administered. Romiplostim, a TPO peptide mimetic, is administered subcutaneously and activates the TPO receptor through binding at the hematopoietic receptor domain. Eltrombopag, a TPO nonpeptide mimetic, is administered orally and activates the TPO receptor by binding at the transmembrane domain. These medications are increasingly used earlier in the course of ITP.

Zhang J, Liang Y, Ai Y, et al. Thrombopoietin-receptor agonists for children with immune thrombocytopenia: a systematic review. *Expert Opin Pharmacother.* 2017;18(15):1543–1551.

169. How is neonatal alloimmune thrombocytopenia diagnosed and treated?

Neonatal alloimmune thrombocytopenia may occur when a fetus expresses platelet antigens inherited from the father that the mother lacks. Some mothers, especially those with "permissive" HLA types, form IgG antibodies that cross the placenta and cause moderate to severe thrombocytopenia in the fetus. First pregnancies can be affected, and there is a high recurrence risk. Both mother and father should be typed for platelet antigens and assessed for incompatibility. In second and subsequent pregnancies at risk, especially when a previous fetus was affected by intracranial hemorrhage, maternal IVIG administration has been demonstrated to be of benefit. Affected infants should receive washed maternal platelets, antigen-matched platelets (most commonly HPA1a negative), or untyped platelets with or without concomitant treatment with IVIG and steroids. Under investigation is whether prenatal platelet typing is of benefit in prevention of the substantial proportion of cases in first pregnancies.

Winkelhorst D, Murphy MF, Greinacher A, et al. Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review. *Blood.* 2017;129(11):1538–1547.

170. In what conditions of children is thrombocytosis most commonly seen?

- Acute infections (e.g., upper and lower respiratory tract infections)
- Chronic infections (e.g., tuberculosis)
- Iron-deficiency anemia
- Hemolytic anemia
- Medications (e.g., vinca alkaloids, epinephrine, corticosteroids)
- Inflammatory disease (e.g., Kawasaki disease)
- Malignancy (e.g., chronic myelogenous or megakaryocytic leukemia)

Chiarello P, Magnolia M, Rubino M, et al. Thrombocytosis in children. *Minerva Pediatr.* 2011;63(6):507–513.

171. What level of thrombocytosis requires treatment?

A high platelet count in most children does not appear to be a cause of significant morbidity because it is often transient. In some centers, aspirin in doses of 81 mg daily are administered when the platelet count exceeds $1.5 \times 10^6/\text{mm}^3$. The early introduction of aspirin therapy may be more important if the patient has other problems that might contribute to hyperviscosity, such as a high WBC count or hemoglobin level.

Denton A, Davis P. Extreme thrombocytosis in admissions to paediatric intensive care: no requirement for treatment. *Arch Dis Child.* 2007;92(6):515–516.

SICKLE CELL DISEASE

172. What is the mutation that results in sickle cell disease?

On the β-globin gene on chromosome 11, the seventeenth nucleotide is changed from thymine to adenine, and thus the sixth amino acid in the β-globin chain becomes valine instead of glutamic acid. Only a single nucleotide substitution is required (GTG for GAG), but the result is sickle hemoglobin (HbS), which polymerizes upon deoxygenation, making the RBC more rigid and causing structural damage to the RBC membrane. This change leads to hemolytic anemia and contributes to vaso-occlusion. Patients who inherit two copies of this mutation have hemoglobin SS sickle cell anemia. It is an autosomal recessive disorder. The α-chain is normal.

Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. *Annu Rev Pathol.* 2019;14:263–292.
Sickle Cell Disease Association of America. www.sicklecelldisease.org. Accessed January 20, 2020.

173. Why is sickle cell disease often asymptomatic during the first months of life?

During the neonatal period, the presence of **large amounts of fetal hemoglobin** reduces the rate of polymerization of HbS and the sickling of RBCs that contain this abnormal hemoglobin. As the amount of fetal hemoglobin decreases after age 3 to 6 months, patients with sickle cell disease are increasingly likely to experience their first clinical manifestations.

174. What are the various genotypes that can cause the clinical syndrome of sickle cell disease?

Genotypes depend on which two genes make up the β chain component. In general, severity varies from SS > $S\beta^0$ – thalassemia > SC > $S\beta^+$ thalassemia > S-hereditary persistence of fetal hemoglobin (HPFH). Hemoglobin concentrations increase from an average of 6 to 8 g/dL with HbSS to 11 to 14 g/dL for HbS-HPFH, which contributes to the variation in clinical severity. Only $S\beta^+$ thalassemia has any hemoglobin A on electrophoresis (5% to 30%).

Ware RE, deMontalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet.* 2017;390(10091):311–323.

175. What are the two major pathophysiologic mechanisms in sickle cell anemia that cause the morbidities associated with the disease?

- **Hemolysis:** Sickled RBCs undergo both intravascular and extravascular hemolysis, which leads to anemia, reticulocytosis, jaundice, gallstones, and occasional aplastic crisis. It now appears that chronic hemolysis affects the utilization and bioavailability of nitric oxide (NO), a potent vasoactive agent. Long-term hemolysis has been associated with pulmonary hypertension and right-sided heart failure.
- **Vaso-occlusion:** Intermittent and chronic vaso-occlusion result in both acute exacerbations (e.g., painful crisis, stroke) and chronic disease manifestations (e.g., retinopathy, renal disease). The adhesion of sickled erythrocytes to inflamed vascular endothelium is a principal pathologic component. Activation of leukocytes and platelets, as well as components of the coagulation cascade, is also prominent.

176. A 6-month-old black male has painful swelling of both hands. What is the most likely diagnosis?

Hand–foot syndrome, or dactylitis. This common early manifestation of sickling disorders in infants and young children is characterized by painful swelling of the hands, feet, and proximal fingers and toes caused by symmetric infarction in the metacarpals, metatarsals, and phalanges (Fig. 9.11). A lack of systemic signs, the presence of symmetric involvement, and young patient age help distinguish hand–foot syndrome from the much less common osteomyelitis, which may also complicate sickle cell disease.

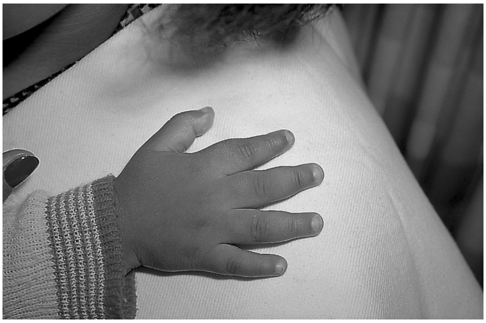

Fig. 9.11 Swelling of the fingers from dactylitis. (From Lissauer T, Clayden G. *Illustrated Textbook of Pediatrics.* London Mosby; 1997:238.)

177. When does functional asplenia occur in children with sickle cell disease?

It may begin as early as 5 or 6 months of age, and it may precede the presence of Howell-Jolly bodies in the peripheral smear. Most children with HbSS who are >5 years old have functional asplenia, with a small, atrophied spleen. Clinical experience indicates that the period of increased risk for serious bacterial infection parallels the development of functional asplenia. Consequently, in addition to routine vaccinations, antibiotic prophylaxis with penicillin is recommended beginning at 2 months of age. Loss of splenic function usually occurs later in patients with HbSC or HbSβ^+ thalassemia or those receiving chronic transfusion therapy.

178. What is the most common cause of death in children with sickle cell disease?

Infection. Splenic dysfunction causes increased susceptibility to meningitis and sepsis (particularly pneumococcal). The incidence of infection can be reduced by 84% with daily penicillin taken orally and initiated early in infancy (by 2 months of age) and continued into childhood. Though studies demonstrated no further benefit after 5 years of age, many providers continue penicillin prophylaxis into the teenage years. Pneumococcal and meningococcal vaccines may provide further protection.

179. How should a child with a vaso-occlusive (painful) event be managed?

For outpatients with an *acute painful crisis,* ibuprofen or acetaminophen and codeine are reasonable choices. Patients with intensely painful crises require day unit or inpatient hospitalization for opioid (including morphine) analgesia, ideally given intravenously. Use of meperidine in this situation is no longer recommended unless the patient has a specific preference for the medication or allergy to other morphine derivatives. Patient-controlled analgesia offers the dual benefit of a constant infusion and intermittent boluses of an analgesic. Other supplementary agents, including nonsteroidal analgesics (e.g., ketorolac), and vasodilators/membrane active agents (e.g., arginine) are under study. For severe crises, blood transfusions to reduce the percentage of sickle cells to $<30\%$ may be beneficial as part of a multimodal pain approach.

Ware RE, de Montalembert M, Tshilolo, Abboud MR. Sickle cell disease. *Lancet.* 2017;390(10091):311–323.

180. A 15-month-old with sickle cell disease presents with pallor and fatigue but no jaundice. On examination, his spleen is palpable to his umbilicus. What is the diagnosis, and how should it be managed?

Acute splenic sequestration represents a true emergency and is the second leading cause of death in young children with sickle cell disease. The clinical problem is primarily one of hypovolemic shock as a result of the pooling of blood in the acutely enlarged spleen. The hemoglobin level may drop to as low as 1 to 2 g/dL. The major therapeutic effort should be directed toward volume replacement with whatever fluid is handy. In most instances, normal saline or colloid solutions will be adequate until properly cross-matched blood is available. Patients may experience “auto-transfusion” where, after a bolus of fluid, the spleen begins to shrink and formerly trapped RBCs reenter the circulation, raising the hemoglobin beyond what one would expect with transfusion or fluids alone. Close monitoring of hemoglobin and repeated assessment of spleen size are critical to ensure the patient does not become polycythemic. Splenectomy may be considered for patients with recurrent splenic sequestration.

Owusu-Ofori S, Remmington T. Splenectomy versus conservative management for acute sequestration crises in people with sickle cell disease. *Cochrane Database Syst Rev.* 2017;11:CD003425.

Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA.* 2014;312(10):1033–1048.

181. A 15-month-old with sickle cell disease presents with pallor and fatigue but no jaundice. He had low-grade fever yesterday and no spleen is palpable. What is the diagnosis, and how should it be managed?

Aplastic crisis. As patients with SCD are dependent on their reticulocyte production to compensate for their ongoing hemolysis and short-lived RBCs, RBC aplasia, often due to infections (parvovirus B19 being one of the most common), may cause a significant, acute drop in hemoglobin by up to 10% to 15% per day. Aplastic crisis is treated with supportive care and blood transfusions until the blood counts stabilize and the reticulocyte count is improving.

182. What is "acute chest syndrome" in sickle cell patients?

Acute chest syndrome refers to the constellation of findings (e.g., fever, cough, chest pain, pulmonary infiltrates) that can resemble pneumonia or pulmonary infarction. The exact mechanism is unknown, and the cause is likely multifactorial. Various infections (e.g., viral, chlamydial, mycoplasmal) may initiate respiratory inflammation, which ultimately causes localized hypoxia; increased pulmonary sickling may then result. Rib and other bone infarcts can also occur, and hypoventilation may result from chest splinting. Pulmonary fat embolism has been seen to occur, particularly in the setting of a preceding bony painful crisis (e.g., the thigh).

Zar HJ. Etiology of sickle cell chest. *Pediatr Pulmon.* 2004;26:S188–S190.

183. How should acute chest syndrome in sickle cell patients be treated?

- **Aggressively** because rapid progression to respiratory failure is possible.
- **Optimization of ventilation** is vital, including supplemental oxygen, analgesics adequate to minimize splinting, incentive spirometry, and other possible measures (e.g., bronchodilators, NO).
- **Judicious hydration:** Overly vigorous hydration can lead to pulmonary edema.
- **Antibiotics:** These should typically be given to cover *Chlamydia, Mycoplasma,* and *Streptococcus pneumoniae*.
- **Blood transfusion,** including erythrocytapheresis (automated RBC exchange transfusion), has been shown to improve the status of patients with acute chest syndrome; this should be considered for patients with severe or worsening disease.

Ware RE, de Montalembert M, Tshilolo, Abboud MR. Sickle cell disease. *Lancet.* 2017;390(10091):311–323.

184. How often is priapism a problem in children with sickle cell disease?

Priapism is an unwanted, painful erection that is usually unrelated to sexual activity. It is an underappreciated morbidity in adolescents with sickle cell disease, usually occurring at least once by the age of 20 years and typically by the age of 12 years. Most patients are unaware of the term and the consequences; early urologic intervention may prevent irreversible penile fibrosis and impotence.

Wang HH, Herbst KW, Rothman JA, et al. Trends in sickle cell disease-related priapism in U.S. children's hospitals. *Urology.* 2016;89:118–122.

185. What are some long-term morbidities associated with sickle cell disease?

- Stroke
- Chronic lung disease
- Renal failure
- Congestive heart failure
- Retinal damage
- Leg ulcers
- Aseptic necrosis of the hip or shoulder
- Poor growth

Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med.* 2017;376(16):1561–1573.

186. How can stroke be prevented in children with sickle cell disease?

Children with sickle cell disease are at increased risk for stroke. The risk for stroke increases and peaks around 2 to 5 years of age then declines, only to increase again in the late teens and throughout adulthood. To prevent initial strokes, children (age 2 to 16 years old) should undergo annual screening with transcranial Doppler ultrasounds (TCDs) to assess flow velocities of the intracranial vessels. Elevated velocities are predictive of increased stroke risk. **Regular blood transfusions** are an effective primary prevention strategy to prevent strokes. The goal of transfusion therapy is to keep the HbS percentage below 30%. Children who have already suffered an overt stroke also benefit from regular transfusions as a secondary prevention method.

Fortin PN, Hopewell S, Estcourt LJ. Red blood cell transfusion to treat or prevent complications in sickle cell disease: an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2018;8:CD012082.

Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med.* 1998;339(1):5–11.

187. If blood transfusions are initiated for primary stroke prevention, when can they be discontinued?

The data are evolving. A multicenter study involving 121 participants found that a subset of patients with a history of abnormal TCD ultrasounds, but limited or no cerebral vasculopathy (as examined by magnetic resonance angiography [MRA]), could safely transition to hydroxyurea (hydroxycarbamide) after at least 1 year of transfusion therapy. It is important to note that it would not be safe to stop transfusions without transitioning to another disease-modifying therapy.

Ware, RE, Davis BR, Schultz WH, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial Doppler flow velocities in children with sickle cell anaemia—TCD with Transfusions Changing to Hydroxyurea (TWiTCH): a multicenter, open-label, phase 3, non-inferiority trial. *Lancet.* 2016;387(10019):661–670.

188. What is the primary mechanism by which hydroxyurea is beneficial for sickle cell disease?

Hydroxyurea is a cytotoxic drug that has been used primarily to treat chronic myelogenous leukemia (CML) and polycythemia vera. However, its use was shown to **increase hemoglobin F (HbF) totals**. It is unclear if this is due to direct effects on γ chain transcription sites or due to preferential γ chain production during erythroid regeneration after cytotoxic insult. Increased concentrations of HbF (particularly $>$20%) are associated with decreased sickling of the RBCs and decreased hemolysis, which results in increased hemoglobin. Clinically, patients experience fewer vaso-occlusive painful events, episodes of acute chest syndrome, transfusion requirements, and hospitalizations. It is unclear if hydroxyurea can prevent or reverse organ damage.

Nevitt SJ, Jones AP, Howard J. Hydroxyurea (hydroxycarbamide) for sickle cell disease. *Cochrane Database Syst Rev.* 2017;4:CD002202.

Platt OS. Hydroxyurea for the treatment of sickle cell anemia. *N Engl J Med.* 2008;358(13):1362–1369.

189. Hydroxyurea treatment in young children: How early and how beneficial?

Infants (9 months to 18 months) have been started on hydroxyurea (maximum dose: 20 mg/kg per day) with minimal toxicity and no increased rate of infection. In a phase 3 randomized controlled trial comparing hydroxyurea to placebo, infants started on hydroxyurea had lower rates of recurrent vaso-occlusive events, dactylitis, acute chest syndrome, transfusion, and hospitalization. TCD velocity rates were also lower, although it is unclear if this translates into decreased risk for stroke. There were no significant differences between the groups in their splenic or renal function.

Schuchard SB, Lissick JR, Nickel A, et al. Hydroxyurea use in young infants with sickle cell disease. *Pediatr Blood Cancer.* 2019 Jul;66(7):e27650.

Ware RE, McGann PT, Quinn CT. Hydroxyurea for children with sickle cell anemia: prescribe it early and often. *Pediatr Blood Cancer.* 2019;30:e27778.

Thornburg CD, Files BA, Luo Z, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood.* 2012;120:4304–4310.

190. How common is the sickle cell trait in the United States?

Heterozygosity for the sickle gene occurs in about 8% of blacks in the United States; 3% of Hispanics in the eastern United States; and a much smaller percentage of individuals of Italian, Greek, Arabic, and Veddah Indian heritage. Also of note is that 2% of blacks in the United States have the hemoglobin C trait.

191. Does sickle cell trait have any significant morbidity?

Under normal physiologic conditions, no significant morbidity is associated with sickle cell trait. RBCs in individuals with sickle cell trait contain only 30% to 40% sickle hemoglobin, which is insufficient to cause sickling. However, in hypoxic settings, sickling may occur. Portions of the kidney may have physiologically low oxygen concentrations that can interfere with function and lead to an inability to concentrate urine (hyposthenuria) and hematuria (usually microscopic and asymptomatic). At high altitudes and in extreme conditions (e.g., when mountain climbing or in an unpressurized aircraft), splenic infarction or cardiac events are possible. Patients with sickle cell trait are also at an increased risk for venous thromboembolism (VTE). Concern does exist of stigmatization of sickle cell trait carriers due to societal misunderstanding of the condition.

Naik RP, Haywood C Jr. Sickle cell trait diagnosis: clinical and social implications. *Hematology Am Soc Hematol Educ Program.* 2015;2015:160–167.

192. After hemoglobin S, what is the second most common worldwide hemoglobin variant?

Hemoglobin E. This variant is particularly high in the Southeast Asian population (especially those of Laotian, Thai, and Cambodian heritage). Heterozygotes are asymptomatic; homozygotes can have a mild microcytic anemia. The most common abnormal findings on a peripheral smear are microcytosis and target cells.

KEY POINTS: SICKLE CELL DISEASE

1. A genetic mutation leads to abnormal β-globin chain that promotes polymerization of hemoglobin and sickling in the setting of hypoxia.
2. Eight percent of blacks in the United States have the sickle cell trait.
3. Acute events include aplastic, hemolytic, vaso-occlusive, and sequestration.
4. The risk for serious bacterial infection is increased among these patients as a result of functional asplenia.
5. Dactylitis (painful hand/foot swelling) is often the earliest manifestation.

THALASSEMIA

193. What are the thalassemias?

The *thalassemias* are a heterogeneous group of disorders of hereditary anemia due to **diminished or absent normal globin chain production**. Normally, four α-globin genes and two β-globin genes are expressed to make the tetrameric globin protein, which then combines with a heme moiety to make the predominant hemoglobin that is found in RBCs, HbA (subunits $\alpha_2\beta_2$). Depending on the number of genes that are deleted, the production of polypeptide chains is diminished. In patients with α-thalassemia, α-globin production is lowered; in patients with β-thalassemia, β-globin production is lowered. When one class of polypeptide chains is diminished, this leads to a relative excess of the other chain. The result is ineffective erythropoiesis, precipitation of unstable hemoglobins, and hemolysis as a result of intramedullary RBC destruction.

Origa R. β-thalassemia. *Genet Med.* 2017;19(6):609–619.
Piel FB, Weatherall DJ. The α-thalassemias. *N Engl J Med.* 2014;371(20):1908–1916.

194. Where was β-thalassemia first described?

Despite its incidence being highest in the Mediterranean region, β-thalassemia was first described by a hematologist, Dr. Denton Cooley, in 1925 in Detroit. Why Detroit and not Europe for the first recognition? Speculation is that the condition was thought to be malaria endemic to that region and with similar clinical features of hemolysis, anemia, and splenomegaly.

Weatherall DJ, Clegg JB. Historical perspectives: the many and diverse routes to our current understanding of the thalassemias. In Weatherall DJ Clegg JB, eds. *The Thalassemia Syndromes.* 4th ed. Oxford: Blackwell Science; 2001:3.

195. What accounts for the variability in the clinical expression of the thalassemias?

Clinical heterogeneity results from variability in the number of gene deletions (particularly in α-thalassemia). As a rule, the greater the number of deletions, the more severe the symptoms. A large number of point mutations have been identified in various populations; this can contribute to the phenotypic diversity. In addition, the coinheritance of other thalassemia genes (e.g., δ-thalassemia) or the persistence of fetal hemoglobin can modify the clinical course.

196. How is the diagnosis of thalassemia made in most clinical laboratories?

Homozygous β-thalassemia is detected by the absence (β^0) or reduction (β^+) of the amount of HbA ($\alpha_2\beta_2$) relative to HbF ($\alpha_2\gamma_2$ or fetal hemoglobin) on hemoglobin electrophoresis. The carrier state for β-thalassemia is characterized by a low mean cell volume and, in most instances, an increased level of HbA2 ($\alpha_2\delta_2$) or HbF. The levels of these two hemoglobins are most accurately measured by column chromatography. Estimation or quantitation from electrophoretic patterns is frequently misleading. The α-thalassemia trait remains a diagnosis of exclusion (low mean cell volume in the absence of an identifiable cause) in the clinical laboratory, although the enumeration of missing α genes for the most common deletions in specific ethnic populations is accomplished by molecular techniques. Newer polymerase chain reaction–based DNA tests for the common variants have become very useful.

197. Describe the clinical features of the α-thalassemia syndromes.

When all four α-globin genes are missing or nonfunctional, this results in severe intrauterine anemia and hydrops fetalis. Extraordinary therapy such as in utero transfusion may result in survival. Absence of three functional α-globin genes results in HbH disease, which is a chronic moderate to severe anemia with jaundice and splenomegaly that may necessitate RBC transfusion therapy. Absence of two α-globin genes is associated with mild microcytic anemia. Absence of one α-globin gene is clinically silent (Table 9.5).

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Table 9.5 Clinical Features of α-Thalassemia

SYNDROME	USUAL GENOTYPE	α GENE NUMBER	CLINICAL FEATURES
Normal	αα/αα	4	Normal
Silent carrier	α-/αα	3	Normal
α-Thalassemia trait	α-/α- or - - /αα	2	Mild microcytic anemia
HbH disease	- - / -α	1	Moderate microcytic anemia Splenomegaly Jaundice

198. What is hemoglobin Barts?

Hemoglobin Barts is a tetramer of γ-chains often noted on the newborn screen due to α-chain deletions. It can be present in varying degrees in the setting of α-thalassemia trait, HbH disease, or fetal hydrops.

199. What are the clinical features of the β-thalassemia syndromes?

- **Thalassemia minor:** Minimal or no anemia (hemoglobin 9 to 12 g/dL); microcytosis; elevated RBC count; no need for transfusion
- **Thalassemia intermedia:** Microcytic anemia with hemoglobin usually >7 g/dL; growth failure; hepatosplenomegaly; hyperbilirubinemia; and thalassemic facies (i.e., frontal bossing, mandibular malocclusion, prominent malar eminences due to extramedullary hematopoiesis) develop between the ages of 2 and 5 years; intermittent or variable transfusion requirements
- **Thalassemia major** (Cooley anemia): Severe anemia (hemoglobin 1 to 6 g/dL) usually during the first year of life; hepatosplenomegaly; growth failure; transfusion dependent

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Olivieri NF. The beta-thalassemias. *N Engl J Med.* 1999;341(2):99–109.

200. How can coexistent iron deficiency increase the difficulty of diagnosing β-thalassemia?

The β-thalassemia trait is usually diagnosed by hemoglobin electrophoresis, with quantitative hemoglobins revealing elevated HbA2 and/or HbF levels. Iron deficiency can cause a lowering of HbA2, thereby masking the diagnosis. With iron replacement, the hemoglobin A2 will rise to the expected elevated levels seen in patients with the β-thalassemia trait.

201. What are the adverse effects of chronic transfusional iron overload in children with thalassemia?

- **Cardiac effects** include congestive heart failure; dysrhythmias; and, less frequently, pericarditis. Cardiac T2* magnetic resonance imaging (MRI) is both diagnostic and prognostic. Significant cardiac iron deposition predicts rates of heart failure and arrhythmia over the subsequent year.
- **Endocrine effects** include delays in growth and sexual development, hypoparathyroidism, and hypothyroidism. Diabetes as a result of iron overload is irreversible, even with intensive chelation.
- **Hepatic effects** include progressive liver fibrosis and cirrhosis. Monitoring with dedicated MRI is recommended.

Kirk P, Roughton M, Porter JB, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation.* 2009;120(20):1961–1968.

202. How do you reduce iron accumulation in children who require repeated transfusions?

- **Chelation therapy:** Subcutaneous or intravenous deferoxamine has been the standard therapy for transfusional overload; however, new oral iron chelators, including daily deferasirox and three-times-daily deferiprone, have demonstrated efficacy as single agents. Studies of combination chelation therapy demonstrate acceptable toxicity profiles with improved iron status.
- **Splenectomy:** This is used primarily in patients with thalassemia (and a small subgroup of patients with sickle cell anemia) who have hypersplenism, which results in the premature destruction of RBCs and increased transfusion requirements.
- **Diet:** Drinking tea with meals reduces dietary iron absorption and may be most helpful in patients with diseases such as thalassemia intermedia, in which the bulk of excessive iron is dietary in origin.
- **Erythrocytapheresis:** Automated erythrocytapheresis (RBC exchange) rather than repeated simple transfusions may markedly reduce transfusional iron loading in patients with sickle cell disease.

Easow Mathew M, Sharma A, Aravindakshan R. Splenectomy for people with thalassemia major or intermedia. *Cochrane Database Syst Rev.* 2016;6:CD010517.

de Dreuzy E, Bhukhai K, Leboulch P, Payen E. Current and future alternative therapies for beta-thalassemia major. *Biomed J.* 2016;39(1):24–38.

Saliba AN, El Rassi F, Taher AT. Clinical monitoring and management of complications related to chelation therapy in patients with β-thalassemia. *Expert Rev Hematol*. 2016;9(2):151–168.

203. In addition to iron loading, what are other risks of chronic transfusion therapy?

Patients on chronic transfusion therapy are at risk for **alloimmunization to RBC antigens**, which may make transfusions a challenge going forward, or HLA antigens, which may make bone marrow transplantation (BMT) a challenge. With every transfusion, patients experience an ongoing risk for transfusion-related infection and experiencing a transfusion reaction.

204. What are the critical steps in planning for a teenager with a chronic hematologic condition to transition to adult-oriented health care?

All teenagers with chronic conditions face challenges when transitioning to adult-oriented health care. Several steps are recommended to ease the transition for these potentially complex patients:

- Begin planning early! Collaborate with the patient and family to create a written health care transition plan by age 14 that includes what services will be needed, who will provide them, and how they will be financed. This should be updated annually until the patient successfully transitions.
- Encourage pediatric patients to begin to assume developmentally appropriate responsibilities for their care (scheduling appointments, calling for refills, etc.).
- Identify a health care professional who assumes responsibility for care coordination and future planning and can partner with the patient and family through the transition to ensure care is uninterrupted.
- Maintain an up-to-date health care summary to communicate the pertinent medical history of the patient to their new providers.

American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. *Pediatrics.* 2002;110(Suppl 3):1304–1306.

205. Do socioeconomic factors affect the ability of pediatric patients to successfully transition health care?

Yes. Patients who live in a low-income household, live in a non–English-speaking household, or are either Hispanic or black are more likely to experience discontinuities in care. Patients with sickle cell disease and other hematologic disorders may be disproportionately affected.

KEY POINTS: THALASSEMIA

1. Normal hemoglobin (HbA): Tetramer of two α and two β chains
2. Associated with quantitative reduction in globin synthesis
3. Homozygous β-thalassemia is most severe form, with pallor, jaundice, hepatosplenomegaly, and growth retardation
4. Expansion of facial bones resulting from extramedullary hematopoiesis
5. Severity of α-thalassemia depends on number of genes deleted (one to four)
6. α-thalassemia: More common among people of Southeast Asian ethnicity
7. β-thalassemia: More common in people of Mediterranean ethnicity

TRANSFUSION ISSUES

206. What is the difference between the direct and indirect Coombs tests?

- *Direct test:* Coombs serum (antihuman globulin) is added directly to a patient's washed RBCs. The occurrence of agglutination means that the patient's RBCs have been coated in vivo by an antibody. The direct Coombs testing is vital for diagnosing AIHAs.
- *Indirect test:* This involves incubating a patient's serum with RBCs of a known type and adding Coombs serum. If sensitization occurs, agglutination will result, which indicates that antibodies in the serum are binding to the antigens on the RBCs. Indirect testing is key for blood cross-matching.

207. What is the difference between forward and reverse blood typing?

A *forward type* determines antigens on patient or donor RBCs. It uses reagent monoclonal antibodies against A or B or Rh(D) and tests for agglutination. A *reverse type* determines antibodies in patient or donor serum or plasma. It tests for agglutination with RBCs of a known phenotype, ensuring the patient has appropriate naturally forming antibodies (anti-A or anti-B isoagglutinins). Outside of the neonatal period (age >4 months), both a forward and a reverse type must be performed for a patient to have a valid ABO type.

208. What is the distribution of blood types in the United States?

This varies by race, but according to American Red Cross data, 40% to 57% are type O, 28% to 40% are type A, 11% to 25% are type B, and 2% to 7% are type AB. Rh negativity ranges from 8% (in type O Caucasian Americans) to 0.1% (in type AB Asian Americans).

American Red Cross. www.redcrossblood.org/learn-about-blood/blood-types. Accessed June 9, 2019.

209. Can a mother with blood type O give birth to a baby with blood type AB?

No (but never say never). Blood group antigens are inherited as dominant traits with one of three alleles (A, B, O) acquired from each parent. Thus a child cannot have a blood group antigen that is not present in one or both parents. A mother with blood type O will have O antigens only; an O-, A-, B- or AB-father cannot pass on both A and B antigens. An O-mother and an AB-father (or the reverse) typically will produce an infant with a blood type of either A or B. If an infant is born with an “impossible” blood type (based on parental testing), the possibilities to consider include (1) incorrect paternity, (2) laboratory error (e.g., mislabeling of cord blood, clerical error, procedural error in the laboratory), or (3) *cis*-AB blood type. *Cis*-AB genotype corresponds to a very rare ABO mutation in which both alleles may come from one parent.

Nickel CP. Incidence of a type AB infant born to a type O mother. *Lab Med.* 2006;37(1):37–39.

210. What can cause a patient to be ABO indeterminate?

Inconsistencies with either the forward or reverse type may cause a patient to be ABO indeterminate. A compatible but out-of-group transfusion may cause the patient to be ABO indeterminate in both the forward and reverse direction. Often, these will result in “mixed field” results where the laboratory notes two populations of cells. Infants <4 months old may not have developed the naturally forming isoagglutinins, so the reverse type may be invalid, and therefore their specimens do not need to be typed. Usually, the reverse type resolves by 6 months to 1 year of age. Leukemia or a history of BMT may cause a patient to be ABO indeterminate. Hypogammaglobulinemia may cause a patient to lack appropriate serum isoagglutinins, causing a discrepancy in the reverse type. In contrast, IVIG infusion, a cold autoantibody, or a cold alloantibody may cause excessive reactivity in the reverse type, thus making the patient ABO indeterminate.

211. How many blood group antigens have been identified?

In addition to the ABO and Rh groups, there are 33 discrete blood group systems (controlled by a single or closely linked group of homologous genes) encompassing **approximately 350 antigens** that have been identified. The most commonly recognized antigens in the Rh group are D, C, c, E, and e, although more than 45 serologically defined Rh antigens have been identified. Other clinically important blood antigentic groups are Kell, Duffy, and Kidd.

Flegel WA. Pathogenesis and mechanisms of antibody-mediated hemolysis. *Transfusion.* 2015;55(Suppl 2):S47–S58.
Daniels G, Reid ME. Blood groups: the past 50 years. *Transfusion.* 2010;50(2):281–289.

212. What is a naturally forming RBC antibody?

RBC alloantibodies are antibodies against RBC antigens that the patient lacks. These are usually only formed after exposure to those antigens through transfusion or pregnancy. However, there are some alloantibodies (such as anti-A and anti-B) that do not require such exposure. This is because similar antigens are widely expressed in nature (e.g., aeroallergens, gut flora) and thus the individual is exposed “naturally.”

213. What is the difference between a type and screen and a type and cross?

When a *type and screen* is performed, both a forward and reverse type are performed on the patient sample. In addition, patient serum or plasma is then incubated with RBCs of a known phenotype to assess for the presence of any alloantibodies. When a *type and cross* is performed, the patient sample has all of the elements of a type and screen performed, but then the plasma or serum of the patient is tested with RBCs of potentially compatible units of blood. If compatible, those units are reserved for the patient.

214. What are the indications for the use of leukoreduced RBCs?

When packed RBCs are prepared from whole blood and then filtered, most of the remaining white cells are removed from the product. Because febrile transfusion reactions are usually the result of leukocytes, filtered products should be used for patients who have experienced such reactions to previous blood transfusions. Filtered RBCs are also effective for reducing the transmission of CMV in at-risk individuals. In addition, the use of filtered blood components reduces the risk for HLA alloimmunization, which is desirable for patients who have undergone repeated transfusions and for those who may need stem cell or solid organ transplants.

215. What is the estimated total blood volume of children?

Estimation of blood volume is dependent on both age and weight. Older children have a lower proportion of their weight as blood compared with younger children. As a rule of thumb, blood volume is estimated as follows:

- Children >3 months of age: 70 mL/kg
- Premature infants: 90 to 100 mL/kg
- Term infants: 80 to 90 mL/kg

Morley SL. Red blood cell transfusions in acute paediatrics. *Arch Dis Child Pract Ed.* 2009;94(3):65–73.

216. What is the RBC transfusion threshold for infants <4 months of age?

There is no easy answer to this question. Transfusion thresholds vary significantly by gestational age, postnatal age, and clinical status because of the complex physiology of neonates and young infants. There is currently a large randomized clinical trial sponsored by the National Institutes of Health (NIH) (Transfusions of Prematures [TOP] trial) comparing restrictive transfusion practices with liberal transfusion practices in preterm infants.

One set of proposed transfusion guidelines is as follows:

- Hct <20% with low reticulocyte count and symptomatic anemia
- Hct <30% requiring oxygen support or significant symptoms, including apnea, bradycardia, tachycardia, or tachypnea
- Hct <35% on >35% oxygen hood or escalated ventilatory support
- Hct <45% on extracorporeal membrane oxygenation (ECMO) or with congenital cyanotic heart disease

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Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr.* 2006;149(3):301–307.
Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion.* 2002;42(11):1398–1413.

217. What is the packed red blood cell (PRBC) transfusion threshold for children >4 months of age?

Transfusion thresholds vary significantly by age and clinical status in older children as well. Restrictive practices are also being evaluated in older children. One study involving 637 children in a pediatric intensive care unit (ICU) found no difference in outcome between using hemoglobin thresholds of 7 g/dL versus 9.5 g/dL as the threshold for transfusion. One set of proposed guidelines is as follows:

- Hct <24% with symptoms of anemia
- Acute blood loss (>15%) unresponsive to other interventions
- Hct <40% on ECMO or severe cardiopulmonary disease
- Sickle cell disease with stroke, acute chest, symptomatic anemia, splenic sequestration, preoperatively for general anesthesia with goal for Hb of 10 g/dL
- Chronic transfusion for patients with failure of RBC production (β-thalassemia, Diamond-Blackfan anemia, etc.) with goal for Hb of 10 to 12 g/dL

Du Pont-Thibodeau G, Tucci M, Ducruet T, Lacroix J. Survey on stated transfusion practices in PICUs. *Pediatr Crit Care Med.* 2014;15(5):409–416.
Lacroix J, Hebert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med.* 2007;356(16):1609–1619.
Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion.* 2002;42(11):1398–1413.

218. In patients with severe chronic anemia, how rapidly can transfusions be given?

When anemia is chronic, there has been cardiovascular adaptation; therefore blood volumes will be relatively normal. Excessively rapid transfusions can lead to congestive heart failure. For patients with a hemoglobin level of <5 g/dL who exhibit no signs of cardiac failure, a safe regimen is to transfuse PRBCs at a rate of 1 to 2 mL/kg per hour by continuous infusion until the desired target is reached. In most patients, 1 mL/kg will raise the hematocrit level by 1%. Judicious use of a diuretic such as furosemide (or automated erythrocytapheresis, in larger children) can be considered.

Jayabose S, Tugal O, Ruddy R, et al. Transfusion therapy for severe anemia. *Am J Pediatr Hematol Oncol.* 1993;15(3):324–327.

219. At typical doses, what are the expected increases and likely average survival of PRBCs, platelets, and FFP?

See Table 9.6.

Table 9.6 Quick Facts About Blood-Product Dosing

PRODUCT	DOSE	EXPECTED INCREASE	SURVIVAL
PRBCs	10-15 mL/kg	10 mL/kg increases Hb by 2-3 g/dL	May persist 60-90 days in circulation
Platelets	10 mL/kg or 1 unit per 5-10 kg	50-100 k/μL	Hours to days
FFP	10-15 mL/kg	1 mL/kg increases factor levels by 1%	4-6 hr

FFP, Fresh frozen plasma; *Hb*, hemoglobin; *PRBCs*, packed red blood cells.

220. What are the indications for platelet transfusion in neonates and children?

Again, transfusion thresholds vary significantly by age and clinical status. One proposed general guideline is as follows:

- Active bleeding in the setting of qualitative platelet defect
- Patient receiving ECMO therapy and platelet count $<$100,000/μL or bleeding
- Platelet count $<$10,000/μL with failure of platelet production
- Platelet count $<$30,000/μL in asymptomatic neonate
- Platelet count $<$50,000/μL in premature infant with active bleeding or requiring invasive procedure
- Platelet count $<$100,000/μL in sick premature infant with active bleeding or requiring invasive procedure

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Sola-Visner M, Bercovitz RS. Neonatal platelet transfusions and future areas of research. *Transfus Med Rev.* 2016;30(4):183–188.
Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion.* 2002;42 (11):1398–1413.

221. What are the components of cryoprecipitate?

Cryoprecipitate is a plasma product of concentrated factors VIII, XIII, vWF, and fibrinogen, which precipitates as FFP is thawed and collected by centrifugation. Indications for use include situations when specific factor concentrates are not available (e.g., hemophilia), reversal of anticoagulation, or DIC. Fibrinogen concentrate is also available for children with congenital fibrinogen deficiencies, including afibrinogenemia and hypofibrinogenemia.

222. What are the most common types of transfusion reactions?

Transfusion reactions occur infrequently, with approximately 2 to 7 events per 1000 units transfused. However, these reactions can be serious and even fatal. The most common transfusion reactions are **allergic transfusion reactions**. Often occurring with plasma containing platelets or FFP, symptoms may range from mild urticaria and pruritus to significant anaphylaxis with hypotension and angioedema. Antihistamines, steroids, or epinephrine may be necessary depending on the severity of the reaction. **Febrile nonhemolytic transfusion** reactions are the second most common, decreasing in frequency due to the use of leukoreduction. Patients experience fever and chills, without evidence of hemolysis, while receiving a transfusion or several hours later. Patients may be treated with antipyretics and meperidine if the chills are significant

223. What is the most common cause of transfusion-related death in the United States?

Transfusion-related acute lung injury (TRALI) is the most common cause of transfusion related death. TRALI is characterized as acute respiratory distress with bilateral lung infiltrates and hypoxia within 6 hours of transfusion. HLA and human neutrophil antigen (HNA) antibodies have been implicated in the pathogenesis of this syndrome.

224. What is the difference between an acute hemolytic transfusion reaction and a delayed hemolytic transfusion reaction?

- *Acute hemolytic transfusion reactions* result in rapid hemolysis during or within 24 hours of an infusion of incompatible blood products. Often, these are due to ABO incompatible transfusions. Patients may experience fever, chills, back pain, and a sense of "impending doom." They may also have hemoglobinuria, which may result in renal failure. Fluids, mannitol, and other supportive care measures may be necessary to treat this type of reaction.
- *Delayed hemolytic transfusion reactions* may occur from 24 hours up to 28 days after transfusion, though they usually present 10 to 14 days after transfusion. These are often due to RBC alloantibody incompatibility. The symptoms may be similar to acute hemolytic reactions, although they are often milder.

225. Why do some blood products require irradiation?

Irradiation with either x-rays or γ irradiation prevents transfusion-associated graft-versus-host disease (TA-GVHD). TA-GVHD is caused by a proliferation of donor T cells within the transfusion recipient that then attack the host. Symptoms include rash, hepatitis, and GI symptoms similar to classic GVHD; however, the hallmark of this disease is pancytopenia. It is greater than 90% fatal when it occurs. Patients at risk for TA-GVHD include patients with known or suspected cellular immunodeficiency; significant immunosuppression due to chemotherapy or BMT; infants $<$1200 g at birth or those who received in utero transfusions; and any patient receiving HLA-matched components, granulocytes, or blood components from directed donors.

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226. In what clinical settings is apheresis utilized?

During *apheresis,* whole blood is removed from the patient and components are centrifugally separated by density: RBCs $>$ WBCs $>$ platelets $>$ plasma. Components are removed as desired, with the remaining components returned to the patient along with replacement fluid or replacement blood products.

- **Red Cell Exchange:** Patient RBCs are removed and replaced with donor PRBCs; this is usually performed on patients with sickle cell disease who want to prevent iron accumulation or who require an acute reduction in their HbS percentage, such as in the setting of acute stroke or acute chest syndrome.
- **Leukocytapheresis:** WBCs are removed; the patient's RBCs, platelets, and plasma are returned along with some fluid; usually this is performed in the setting of acute leukemia with elevated WBC and signs or symptoms of leukostasis ($>$100, 000/μL in acute myelogenous leukemia [AML], $>$200,000 to 250,000/μL in acute lymphoblastic leukemia [ALL], and $>$400,000/μL in CML).
- **Therapeutic Plasma Exchange:** Plasma is removed; all cellular components are returned to the patient, often with 5% albumin and saline as replacement fluid; replacement with FFP can be used if patients have a coagulopathy or when plasmapheresis is performed for certain conditions, such as thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome.
- **Thrombocytapheresis:** Platelets only are removed; usually only performed after platelet count is $>$1,500,000/μL; not usually performed in pediatrics.

227. How are transfusion-transmitted diseases prevented?

Direct testing and **donor screening/deferral**. Direct testing of blood products includes serologic testing for the presence of antibodies to known pathogenic antigens and nucleic acid amplification testing (NAAT), which detects viral DNA/RNA. All blood products or donors are tested using either or both of the previous methods for HIV, hepatitis B, hepatitis C, HTLV-I/II, syphilis, West Nile virus, Zika, and *Trypanosoma cruzi*. With implementation of NAAT testing, the window for HIV detection has been reduced to 9 days and the window for hepatitis C to $<$8 days. Transfusion-transmitted diseases without an FDA-approved donor screening test, such as malaria and prion diseases, are prevented through donor screening questions and donor deferrals.

228. What role does molecular testing play in providing blood products to patients?

Molecular phenotyping of RBC antigens, which currently uses single-nucleotide polymorphisms (SNPs) to predict antigen phenotype, is an exciting and expanding area of transfusion medicine. This technology is able to identify the expected phenotype of a patient's or donor's RBCs at multiple ($>$30) antigens from DNA. This can be used to identify donors with rare RBC phenotypes to be added to the American Rare Donor Program (ARDP). It can also be used in clinical practice to allow for better matching of RBC products and to clarify serologic ambiguities.

Acknowledgment

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INFECTIOUS DISEASES

Marc D. Foca, MD

ANTI-INFECTIVE THERAPY

KEY POINTS: ANTI-INFECTIVE THERAPY

1. Formal allergy testing is frequently negative in patients who report a penicillin allergy.
2. Rashes seen with viral or bacterial illnesses may confound a history of antibiotic allergy.
3. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a prevalent pathogen in the community, and empiric therapy for certain infections may be broadened to include MRSA coverage.
4. Antibiotic resistance is emerging in all types of organisms, risking the use of drugs that are safe and approved for use in the pediatric population.

1. What are the common features of penicillins?

Penicillins are among the earliest classes of antibiotics developed. They are derived from the fungus *Penicillium* and share a core structural feature—a β-lactam ring—with other classes of antibiotics, such as cephalosporins and carbapenems. Penicillins interfere with the peptidoglycan cross-linking that is required to produce stable bacterial cell walls. They are not active against organisms that are cell wall deficient, such as *Chlamydia* and *Mycoplasma* species.

2. Why are penicillins useful in children with meningitis if penicillins do not readily cross the blood–brain barrier?

Penicillins penetrate most tissue spaces well but do not normally cross the blood–brain barrier except in the case of inflamed meninges, as in meningitis. They have a high therapeutic index, and doses can be escalated to increase tissue and CNS penetration.

3. What are the different classes and spectra of activity of penicillins?

Penicillins (penicillins G [intravenous] and V [oral]):

- These are natural penicillins that are derived directly from the *Penicillium* mold. These drugs are active against most nonpenicillinase (a specific β-lactamase that hydrolyzes the β-lactam ring) producing gram-positive cocci and gram-positive anaerobic organisms.
- Penicillin G is the drug of choice for *Treponema pallidum* infection (syphilis) and *Streptococcus agalactiae* (also known as group B streptococcus).
- Penicillins are also the treatment of choice for group A streptococcal pharyngitis and some anaerobic infections.

Antistaphylococcal penicillins are also called ***penicillinase-resistant penicillins*** (methicillin, oxacillin, nafcillin, and dicloxacillin [oral]):

- These have side chains attached to the penicillin β-lactam ring that inhibit their inactivation by antistaphylococcal penicillinases.
- They display excellent activity against sensitive strains of *Staphylococcus aureus* and should be used whenever possible instead of vancomycin, which has less staphylococcal activity.
- The bulky side chains also limit penetration of these drugs through the cell membrane, giving them a narrow spectrum of action.

Aminopenicillins (ampicillin and amoxicillin):

- The spectrum is similar to that of penicillin but includes additional activity against aerobic gram-negative bacteria (e.g., *Escherichia coli* and *Salmonella* spp.) and gram-positive bacteria (e.g., *Listeria*).
- Many previously susceptible gram-negative organisms are now resistant to the aminopenicillins.

Extended spectrum, also described as "antipseudomonal penicillins" (piperacillin and ticarcillin):

- These have an expanded gram-negative spectrum and can be used to treat susceptible strains of *Pseudomonas aeruginosa* and *Proteus* spp.

Combinations with β-lactamase inhibitors:

- The spectrum of certain penicillins can be enhanced by the addition of a β-lactamase inhibitor. β-Lactamases are a common basis for penicillin resistance in some bacteria. Common combinations include amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, and ticarcillin-clavulanate, which extend their activity to cover *Haemophilus influenza, Bacteroides fragilis,* and some *Enterobacteriaceae* (enteric gram-negative organisms).

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4. In patients for whom the history lists "penicillin allergy," how commonly is a true allergy present on testing?

A true allergy is present on testing $\leq$**10%** of the time. In patients reporting a penicillin allergy, skin tests and radioallergosorbent (RAST) tests are frequently negative (positive $\leq$20% and $\leq$3%, respectively). Much of the confusion arises from the use of the term *allergic reaction* to describe a gamut of nonimmunologic adverse experiences that may be attributable to either the medication, the underlying disease process, or an interaction of the two.

Norton AE, Konvinse K, Phillips EJ, Broyles AD. Antibiotic allergy in pediatrics. *Pediatrics.* 2018;141(5):e20172497.

5. If a 16-year-old male develops a pruritic, maculopapular rash 1 week after starting treatment with amoxicillin for an exudative pharyngitis, should he be designated as "amoxicillin allergic"?

No! As previously mentioned, the immune response that is mounted to a viral pathogen may alter the immune response to antimicrobials, creating an "allergic reaction" that is unique to the organism and drug at hand. The classic example of this is the development of a rash after treatment with amoxicillin in patients with Epstein-Barr virus (EBV). Recent reports have implicated the virus itself in addition to the interaction of the virus and the antimicrobial agent. In addition, many herpes viruses (such as EBV and human herpesvirus 6), as well as enteroviruses, will cause a maculopapular eruption as part of the viral syndrome. These patients are not allergic to penicillins. This should also be taken as further incentive to avoid prescribing antimicrobials for viral illnesses.

6. What are the similarities between penicillins and cephalosporins?

Both cephalosporins and penicillins are derived from fungi: cephalosporins are from the fungus *Acremonium* (formerly *Cephalosporium*), and penicillin is from the *Penicillium* fungus. Furthermore, they both contain a β-lactam ring and interfere with bacterial cell wall synthesis by irreversibly inhibiting penicillin-binding protein peptidoglycan cross-linking.

7. How do the "generations" of cephalosporins differ from one another?

Cephalosporins are divided into four "generations" based on the antimicrobial spectrum of action; in general, activity against gram-negative organisms increases with increasing generation, whereas activity against gram-positive organisms decreases with each generation. Third- and fourth-generation cephalosporins have good penetration in the cerebrospinal fluid (CSF).

8. What are the differences among first-, second-, third-, and fourth-generation cephalosporins?

First-generation cephalosporins (e.g., cefazolin, cephalexin, cefadroxil)

- Good activity against gram-positive organisms (especially methicillin-susceptible *S. aureus* and streptococcal spp.)
- Frequently used as prophylaxis for orthopedic, cardiovascular, head and neck, and many types of neurosurgical or general surgical procedures (i.e., herniorrhaphy)
- May have activity against some *Escherichia coli* and *Klebsiella* species, but lack efficacy against *Haemophilus influenza*
- May be considered as alternatives to penicillins for the treatment of group A streptococcal pharyngitis and group B streptococcal (GBS) prophylaxis during labor.

Second-generation cephalosporins (e.g., cefuroxime, cefotetan, cefoxitin)

- Increased spectrum of activity, including many gram-negative organisms
- Increased activity against *B. fragilis*
- Prophylaxis for intra-abdominal infections (e.g., cefotetan, cefoxitin)
- Treatment for nosocomial pneumonia
- No antipseudomonal activity

Third-generation cephalosporins (e.g., ceftriaxone, cefotaxime, cefixime, cefdinir, ceftazidime)

- Broad spectrum, excellent activity against gram-negative bacteria
- Generally less activity against gram-positive organisms, such as methicillin-susceptible *S. aureus,* than earlier generations.
- Very high blood and CSF levels achievable in relation to minimal inhibitory concentration for bacterial strains
- Wide therapeutic index with generally minimal toxicity (similar to previous generations)
- Some offer single-daily dosing
- Ceftazidime: the first cephalosporin with antipseudomonal coverage
- More expensive

Fourth-generation cephalosporins (e.g., cefepime)

- Broadest spectrum, with activity against most staphylococcal and streptococcal species (but NOT methicillin-resistant *S. aureus*) and gram-negative organisms, including *Pseudomonas* spp.
- Crosses into the CSF
- No activity against anaerobic organisms

Harrison CJ, Bratcher D. Cephalosporins: a review. *Pediatr Rev.* 2008;29(8):264–272.

9. Is there a fifth-generation cephalosporin?

Ceftaroline, which has bactericidal activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-intermediate *S. aureus* (VISA) strains, as well as some gram-negative pathogens. It is approved by the Food and Drug Administration (FDA) for children ≥ 2 months for treatment of acute bacterial skin and soft tissue infections (SSTIs) and community-acquired pneumonia. Another fifth-generational cephalosporin, ceftobiprole, is awaiting FDA approval.

Yim J, Molloy LM, Newland JG. Use of ceftaroline fosamil in children: review of current knowledge and its application. *Infect Dis Ther.* 2017;6(1):57–67.

10. Can cephalosporins be safely given to patients who are allergic to penicillin?

Previous estimates of cross-sensitivity to cephalosporins among penicillin-allergic patients were thought to be 8% to 18%, but these rates have been criticized as inaccurate and excessive. Side-chain–specific antibodies appear to be key in the immune response to cephalosporins. The incidence of allergic cross-reactivity varies with the chemical side-chain similarity of the cephalosporin to penicillin or amoxicillin. For first-generation cephalosporins, the attributable increased risk is thought to be only 0.4%. For certain second- and third-generation cephalosporins (e.g., cefuroxime, cefpodoxime, and cefdinir), the risk is thought to be close to zero. No evidence supports an increase of anaphylaxis with cephalosporins among penicillin-allergic patients. The American Academy of Pediatrics (AAP) guidelines do endorse the use of selected second-generation and third-generation cephalosporins for penicillin-allergic patients as long as the penicillin reaction is not severe.

Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. *J Emerg Med.* 2012;181(5):612–620.

Pichichero M. A review of the evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics.* 2005;115(4):1048–1057.

11. What are the two primary mechanisms of resistance to β-lactam antibiotics?

- **Penicillin-binding proteins (PBPs)**: PBPs are enzymes responsible for the cross-linking between glycan chains and are the target proteins for β-lactam antibiotics. Mutational alterations in PBPs can confer resistance by reducing binding of a β-lactam antibiotic to the active site. This mechanism can be overcome by a higher dose of the antibiotic.
- **β-Lactamases**: These are enzymes that hydrolyze the β-lactam ring of the antibiotic. The genes encoding these enzymes may be inherently present on the bacterial chromosome or may be acquired via plasmid transfer. Certain types of β-lactamase gene expression may be induced by exposure to β-lactams; for example, the genes encoding these β-lactamases are found in the chromosomes of organisms such as *Serratia, Pseudomonas, Acinetobacter, Citrobacter,* and *Enterobacter* (often labeled the "SPACE" organisms). This mechanism of resistance, in general, cannot be overcome simply by using a higher dose of drug.

12. What are the main features of carbapenems?

Carbapenems are β-lactam antibiotics that also bind PBPs, disrupting the growth and structural integrity of bacterial cell walls. They provide gram-positive as well as enhanced anaerobic and excellent gram-negative coverage compared with other β-lactams. They are also resistant to most β-lactamases, including so-called extended-spectrum β-lactamases (ESBLs), but they are susceptible to β-lactamases known as metallo-β-lactamases. They do not cover MRSA.

13. When should "double antimicrobial coverage" be used?

Synergy occurs when the combination of two antibiotics has a greater killing effect than the sum of the two drugs given separately (i.e., the effect is super-additive: $2 + 2 = 5$). In general, the use of two drugs has not been shown to be better than a single drug that appropriately targets the causative organism and site of infection. One exception to this is infective endocarditis, where the use of two or more drugs is recommended in most circumstances. Another role for the use of more than one drug is in an unstable patient for whom there is a high suspicion of an infection with an antibiotic-resistant organism. Empiric therapy with more than one drug to cover "gaps" in sensitivities is often appropriate. Therapy can then be narrowed if an organism is isolated or as the patient improves.

14. What are the "ESKAPE" organisms?

The bacteria *Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. aeruginosa,* and *Enterobacter* species are sometimes referred to as the "ESKAPE" organisms, which emphasizes that they are major causes of nosocomial (and increasingly community-acquired) infections and have developed mechanisms to "escape" the effects of many antimicrobials. In addition to MRSA, vancomycin-resistant *E. faecium* (VRE), *Acinetobacter* species, multidrug-resistant (MDR) *P. aeruginosa,* carbapenem-resistant *Klebsiella* species, and *E. coli* are emerging as significant pathogens in both the United States and other parts of the world.

Pendleton JN, Gorman SP, Gilmore BF. Clinical relevance of the ESKAPE pathogens. *Expert Rev Anti Infect Ther.* 2013;11(3):297–308.

Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48(1):1–12.

15. How can the emergence of antibiotic-resistant pathogens be minimized?

- Appropriate hand hygiene, contact isolation, and environmental decontamination to reduce the transmission of resistant organisms to other patients
- Use of the most potent, narrowest-spectrum antibiotic possible for an appropriate length of time
- Minimization of the empiric use of broad-spectrum antibiotics
- Avoidance of antibiotic treatment of illnesses that are likely viral
- Awareness of local antibiotic resistance patterns

16. What is the distinction between community-associated MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA)?

MRSA was first reported in 1961 and was described for the next three decades as primarily a nosocomial pathogen. A report describing the deaths of four previously healthy children in the Midwestern United States in 1998 brought attention to the issue of MRSA infections in the general population, and CA-MRSA was recognized as a distinct clinical entity.

The most commonly accepted definition of CA-MRSA, as put forth by the Centers for Disease Control and Prevention (CDC), is the diagnosis of MRSA in the outpatient setting or within 48 hours of hospital admission and a lack of risk factors for chronic medical conditions. However, the source of the infection, the antibiotic phenotype, and the genotype of the organism have all been ways to differentiate CA-MRSA from HA-MRSA. Practically, these definitions and distinctions are becoming less relevant as the epidemiology of MRSA and its resistance patterns change and expand. In many locations, strains historically classified as CA-MRSA now cause a majority of nosocomial disease. As molecular typing methods advance, it is likely that the terms CA-MRSA and HA-MRSA will become obsolete and be replaced with more descriptive terms for both the local and global strains of MRSA.

Mediavilla J, Chen L, Mathema B, Kreiswirth BN. Global epidemiology of community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA). *Curr Opin Microbiol.* 2012;15(5):588–595.

Chua K, Laurent F, Coombs G, Grayson ML, et al. Antimicrobial resistance: not community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA)! A clinician's guide to community MRSA — its evolving antimicrobial resistance and implications for therapy. *Clin Infect Dis.* 2011;52(1):99–114.

17. Why is the D-test done?

The *D-test* is done with MRSA isolates that are susceptible to clindamycin and resistant to erythromycin to evaluate whether that isolate might have resistance not constitutively expressed (i.e., always produced) but *inducible by exposure to macrolides*. If patients with this type of MRSA are treated with clindamycin, they may have a higher likelihood of treatment failure or recrudescence. The test involves placing antibiotic disks for erythromycin and clindamycin in close proximity on the agar plate. A flattening of the clindamycin zone of bacterial growth adjacent to the erythromycin disk produces a "D" appearance and indicates the MRSA isolate has inducible resistance to clindamycin (Fig. 10.1).

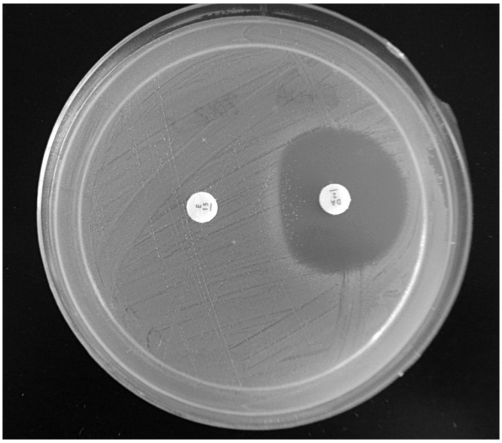

Fig. 10.1 D-test showing flattened zone of clindamycin near the erythromycin disk, demonstrating erythromycin-induced clindamycin resistance. (From Mohapatra TM, Shrestha B, Pokhrel BM. Constitutive and inducible clindamycin resistance in Staphylococcus aureus and their association with methicillin-resistant S. aureus (MRSA). *Int J Antimicrob Agents.* 2009;33:188).

18. Is mupirocin useful in the eradication of *S. aureus* in colonized children?

Colonization of the nasal mucosa or skin is common in children. About 15% to 40% of healthy children are carriers of methicillin-sensitive *S. aureus* (MSSA). MRSA nasal carriage ranges from 1% to 24% in various studies involving day care, emergency room visits, or hospitalized children. The use of mupirocin applied two to three times daily for 1 to 21 days was shown in some adult studies to significantly but variably decrease colonization and recurrent invasive disease. However, eradication is difficult and typically involves additional measures, such as chlorhexidine baths, stringent cleaning of the home environment, and often decolonization of the family as well. Unfortunately, recolonization is common. Protracted use of mupirocin leads readily to increased rates of mupirocin resistance in both MSSA and MRSA isolates. Thus mupirocin is not recommended for routine use in otherwise healthy children to decrease colonization. In certain special circumstances, such as patients with frequent SSTIs and underlying medical conditions (e.g., severe eczema, acquired or congenital immunodeficiencies, and elective surgery), decolonization may be warranted.

McNeil JC, Fritz SA. Prevention strategies for recurrent community-associated *Staphylococcus aureus* skin and soft tissue infections. *Curr Infect Dis Rep.* 2019;21(4):12.

Liu Z, Norman G, Iheozor-Ejiofor Z, et al. Nasal decontamination for the prevention of surgical site infection in *Staphylococcus aureus* carriers. *Cochrane Database Syst Rev.* 2017;5:CD012462.

Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis.* 2011;52(3):285–292.

19. What is the "red man syndrome," and which antibiotic is it associated with?

The *red man syndrome* is a frequent occurrence with the rapid infusion of **vancomycin** (although there are reports of red man syndrome from ciprofloxacin, rifampin, and amphotericin B) and is characterized by flushing of the neck, face, and thorax. Patients commonly complain of diffuse burning, itching, and dizziness and can develop fever and paresthesias around the mouth. Histamine release from degranulation of mast cells underlies this reaction; however, it is not mediated by immunoglobulin E (IgE) and therefore does not represent a true hypersensitivity reaction. Generally, the reaction appears in the first 10 minutes of administration and can be avoided by slowing the rate of drug infusion. Administration of an H1-receptor antagonist (e.g., diphenhydramine) before vancomycin is given is also effective for preventing this reaction.

20. How should infections with VRE be managed?

Resistance to vancomycin has been observed in *E. faecium* and, less commonly, *Enterococcus faecalis*. These infections are acquired nosocomially, which reflects the fact that the organism can survive on inanimate surfaces (including medical equipment) for weeks. They occur more commonly with prolonged use of antibiotics. Basic tenets of anti-infective therapy apply: foreign bodies should be removed, infected fluid collections should be drained, and patients should be placed on contact isolation to prevent spread. The oxazolidinone antibiotic linezolid has shown some effectiveness, but the data are limited. The combination streptogramin agent quinupristin-dalfopristin is approved for individuals $\geq$16 years of age, and dosing guidelines for children $\geq$12 years of age are available. It is noteworthy that quinupristin-dalfopristin has activity against *E. faecium* but not *E. faecalis*, and it has many drug interactions, which limits its use in certain situations. Daptomycin and newer cephalosporins, including ceftaroline, have direct or synergistic activity against these organisms as well, but there is less experience with their use in pediatric populations.

Contreras GA, Munita JM, Arias CA. Novel strategies for the management of vancomycin-resistant enterococcal infections. *Curr Infect Dis Rep.* 2019;21(7):22.

Patel R, Gallagher JC. Vancomycin-resistant enterococcal bacteremia pharmacotherapy. *Ann Pharmacother.* 2015;49(1):69–85.

21. In what situations may treatment with vancomycin be considered appropriate?

- Serious infections (e.g., meningitis, endocarditis) attributable to β-lactam–resistant, gram-positive organisms (e.g., coagulase-negative *Staphylococcus* spp., MRSA, some enterococci spp.)
- Neonates, immune-compromised, or ill-appearing children with risk factors for invasive disease, such as the presence of an indwelling central venous device
- Infections attributable to gram-positive microorganisms in patients with serious allergies to β-lactam antibiotics
- Prophylaxis, as recommended by the American Heart Association, for endocarditis in certain high-risk patients
- Prophylaxis for certain procedures (e.g., implantation of prosthetic materials or devices) at institutions with high rates of MRSA
- Enterally administered vancomycin is indicated for antimicrobial-associated colitis (e.g., *Clostridium difficile,* especially the NAP-1 strain) that fails to respond to metronidazole or is life threatening.

American Academy of Pediatrics. Antimicrobial agents and related therapy. In Pickering LK, ed. *2012 Red Book: Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Park, IL: American Academy of Pediatrics; 2012:805–806.

22. Are fluoroquinolones safe to use in children?

Members of the fluoroquinolone class of antibiotics act against bacterial DNA gyrase and topoisomerase II, two enzymes that are required for bacterial DNA replication. No member of the class is approved by the FDA for *routine* use in patients <18 years. Part of the basis for this recommendation is the occurrence of arthropathy in immature beagle dogs treated with ciprofloxacin or other quinolones. However, there is growing experience with the use of these antibiotics in adolescents and children, primarily those with cystic fibrosis in whom endogenous *P. aeruginosa* strains may display high-level resistance to other antibiotic classes (e.g., antipseudomonal penicillins, carbapenems, aminoglycosides). FDA-approved pediatric indications for ciprofloxacin include postexposure treatment for inhalation anthrax, treatment of plague, and topical therapy for conjunctivitis. The AAP endorses the use of ciprofloxacin as oral therapy for urinary tract infection (UTI) and pyelonephritis caused by *P. aeruginosa* or other MDR gram-negative bacteria in children aged 1 through 17 years when alternative agents are unavailable. Fluoroquinolones may also be considered when parenteral therapy is not feasible and the infection is caused by MDR organisms for which there are no other effective oral agents available.

American Academy of Pediatrics. Antimicrobial agents and related therapy. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:904–905.

23. What are the indications for ribavirin?

Ribavirin is a guanosine analog that inhibits RNA polymerase and subsequently RNA synthesis. It was originally developed in 1972 and was used in the 1980s and 1990s as an inhaled therapy against respiratory syncytial virus (RSV). Both cohort and trial data failed to prove a benefit in mortality or ventilator days in mechanically ventilated infants who had been previously well. However, cohort data have shown that both the oral and the IV forms may be of use to prevent lower tract spread of upper tract disease and mortality in allogenic stem cell transplant patients. Most recently, it has shown activity against hepatitis C and is an approved therapy in children in combination with peginterferon gamma, although newer direct-acting agents probably have improved activity and less toxicity. Ribavirin also has activity against certain viral hemorrhagic fevers and is used to treat Lassa virus infections.

American Academy of Pediatrics. Hepatitis C and hemorrhagic fevers. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:383, 385, 978t.

24. Why is chicken soup so helpful for upper respiratory infections (URIs)?

The benefits of chicken soup have been lore for hundreds of years, beginning in the twelfth century, when physician and philosopher Maimonides extolled its virtue. The precise mechanisms of its anecdotal therapeutic benefits remain elusive. A 2000 study at the University of Nebraska found that the nonparticulate component of chicken soup in vitro inhibited neutrophil migration in a concentration-dependent manner. A component of chicken soup, the dipeptide carnosine, may offer protection against reactive oxygen radical species–dependent injury. These anti-inflammatory effects may be some of the mechanisms by which chicken soup mitigates the symptoms of URIs. Of course, placebo effects should not be minimized.

Babizhayev MA, Deyev AI, Yegorov YE. Non-hydrolyzed in digestive tract and blood natural L-carnosine peptide ("bioactivated Jewish penicillin") as a panacea of tomorrow for various flu ailments. *J Basic Clin Physiol Pharmacol.* 2013;24(1):1–26.

Rennard BO, Ertl RF, Gossman GL, et al. Chicken soup inhibits neutrophil chemotaxis in vitro. *Chest.* 2000;118(4):1150–1157.

25. Is there any physiologic basis to the adage "starve a fever, feed a cold"?

Some studies indicate that anorexia increases the number of type 2 T helper (Th2) cells, which are key in fighting bacterial infections. This would serve as a potentially useful behavioral adaptation, particularly in preantibiotic times. Eating, on the other hand, promotes type 1 T helper (Th1) cells by gastrointestinal (GI) stimulation of vagal and neurohormonal factors. The Th1 cells are essential components of the antiviral immune reaction, which might include rhinoviruses and others involved in the common cold. Fluids should never be limited in children with fever.

Bazar KA, Yun AJ, Lee PY. "Starve a fever and feed a cold": feeding and anorexia may be adaptive behavioral modulators of autonomic and T helper balance. *Med Hypotheses.* 2005;64(6):1080–1084.

van den Brink GR, van den Boogaardt DE, van Deventer SJ, Peppelenbosch MP. Feed a cold, starve a fever? *Clin Diagn Lab Immunol.* 2002;9(1):182–183.

CLINICAL ISSUES

26. What are the three stages of pertussis infection (whooping cough)?

1. **Catarrhal** *(may last 1 to 2 weeks)*: This stage is characterized by low-grade fever, URI symptoms, mild cough, and apnea in infants.

2. **Paroxysmal** *(may last 1 to 6 weeks)*: Symptoms include severe cough occurring in paroxysms and onset of inspiratory “whoop.”
3. **Convalescent** *(may last 2 to 3 weeks)*: Resolution of symptoms occurs; however, coughing fits may persist. Because of the protracted nature of the disease, it is called the “hundred-day cough” in China.

27. What is the most common cause of death in children with whooping cough?

Almost one-quarter of infants and children will contract pneumonia, and approximately 2% will die from whooping cough. Ninety percent of deaths are attributable to **pneumonia**, which most often develops as a secondary bacterial infection. These cases can be easily missed during the paroxysmal phase, when respiratory symptoms are so prominent and usually attributed solely to pertussis. A new spiking fever should prompt a careful search for an evolving pneumonia.

28. Is antibiotic therapy of value in pertussis infection?

If used during the first 14 days of illness or before the paroxysmal stage, macrolide antibiotics such as erythromycin, clarithromycin, and azithromycin can decrease the severity of symptoms during the paroxysmal stage and help prevent transmission of the illness. If the diagnosis is established later in the course, these antibiotics should still be administered to eliminate the nasopharyngeal carriage of *Bordetella pertussis* and limit the spread of disease. Evidence suggests that treatment with macrolides is effective for eradicating carriage and preventing transmission.

29. What are ways on physical examination to help distinguish swelling as a result of mumps from swelling caused by lymphadenitis?

- *Hatchcock sign*: Upward pressure applied to the angle of the mandible produces tenderness with mumps; this maneuver produces no tenderness with adenitis.
- Have the patient sip on lemon juice or suck a lemon wedge. Stimulation of salivation will cause pain in mumps with enlargement of the parotid gland, but no change is noted in patients with adenitis.
- As swelling progresses, the angle of the jaw is obscured. In mumps, when the patient is viewed from behind, the ear lobe is commonly lifted upward and outward.
- With enlargement of the parotid gland, the parotid gland remains in its anatomic relationship with the long axis of the ear, but lymphoid enlargement typically is posterior (Fig. 10.2).

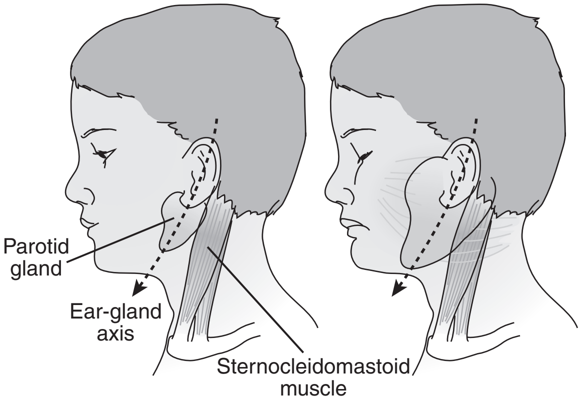

Fig. 10.2 A parotid gland infected with mumps *(right)* compared with a normal gland *(left)* in this schematic drawing. An imaginary line bisecting the long axis of the ear divides the parotid gland into two equal parts. In mumps, these anatomic relationships are not altered, but in lymphadenitis, an enlarged cervical lymph node is usually posterior to the imaginary line. (From Kleigman RM, Stanton BF, Schor NF, et al. *Nelson Textbook of Pediatrics.* 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:1079.)

30. What is the empiric treatment of an SSTI in the setting of the increasing prevalence of CA-MRSA?

As with any SSTI, the principle of incision and drainage (I & D) of localized collections should prevail. In pediatric patients, data suggest that skin abscesses in the immunocompetent host will be adequately treated with I & D alone, without adjuvant antibiotic therapy. Whenever possible, specimens should be obtained for culture and susceptibility testing. For children with minor skin infections (such as impetigo), mupirocin 2% topical ointment can be used. Some authorities have suggested a change in empiric antibiotic therapy to include MRSA coverage is warranted when the patient-specific population prevalence of CA-MRSA infection exceeds 10% to 15%. However, in some communities, there is increasing resistance of both MRSA and MSSA to clindamycin and emerging resistance to trimethoprim-sulfamethoxazole. In hospitalized children with SSTI, empiric vancomycin is recommended. In patients who are clinically stable and do not have bacteremia and/or additional intravascular focus, empiric or step-down therapy with clindamycin may be started.

Fenster DB, Renny MH, Ng C, Roskind CG. Scratching the surface: a review of skin and soft tissue infections in children. *Curr Opin Pediatr.* 2015;27(3):303–307.

Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis.* 2011;52(3):285–292.

31. What are the distinguishing features of staphylococcal scalded skin syndrome, staphylococcal toxic shock syndrome, and streptococcal toxic shock syndrome?

See Table 10.1.

Table 10.1 Distinguishing Features of Staphylococcal Scalded Skin Syndrome, Staphylococcal Toxic Shock Syndrome, and Streptococcal Toxic Shock Syndrome

CLINICAL FEATURES	STAPHYLOCOCCAL SCALDED SKIN SYNDROME	STAPHYLOCOCCAL TOXIC SHOCK SYNDROME	GROUP A STREPTOCOCCAL TOXIC SHOCK-LIKE SYNDROME
Organism	*Staphylococcus aureus*	*Staphylococcus aureus*	Group A streptococci
	Usually phage group 11, type 71	Usually phage group 1, type 29	Usually type 1, 3, or 18
			Exotoxin A production
Site of infection	Usually focal	Mucous membranes	Blood, abscess, pneumonia, empyema, cellulitis, necrotizing fasciitis
	Mucocutaneous border: nose, mouth, diaper area	Infected wound or furuncle	
	Sometimes inapparent	Sometimes inapparent	Sometimes inapparent
Skin rash	Tender erythroderma: face, neck, generalized	Tender erythroderma: trunk, hands, feet	Erythroderma: trunk, extremities
	Bullae, no petechiae	Edema of hands, feet	
Desquamation	Early, first 1-2 days, generalized, feet	Late, 7-10 days, mostly hands and feet	Late, 7-10 days, mostly hands
		Hyperemia of oral and vaginal mucosa	Hyperemia of oral and vaginal mucosa
Mucous membranes	Normal	Hypertrophy of tongue papillae	Hypertrophy of tongue papillae
Conjunctivae	Normal	Markedly injected	Injected
Course	Insidious, 4-7 days	Fulminant, shock with secondary multiorgan failure, 10% mortality	Fulminant, shock with early primary multiorgan failure, 30%-50% mortality
	Benign, <1% mortality		

Adapted from Bass JW. Treatment of skin and skin structure infections. *Pediatr Infect Dis J.* 1992;11(2):152–155.

32. Can antiviral medications be used to prevent or treat oral herpes simplex virus (HSV) infections?

In immunocompetent hosts, oral acyclovir or valacyclovir offers *significant therapeutic benefit* in primary HSV gingivostomatitis but has *limited efficacy* for the treatment of recurrent herpes labialis. Valacyclovir is the prodrug of acyclovir, meaning it is converted to acyclovir after absorption. Valacyclovir achieves higher plasma levels of acyclovir than oral preparations of acyclovir and is dosed less frequently, making it the agent of choice. Topical antivirals have not shown consistent benefit in either of these settings. Prophylaxis with valacyclovir can reduce the number of recurrences in adults (especially pregnant women) with herpes labialis, but it has not been well studied in children.

33. What is the proper medical term for oral thrush?

Acute pseudomembranous candidiasis is the proper medical term for oral thrush—quite a mouthful. Although thrush is sometimes confused with residual formula in the mouth in infants, formula is more easily removed with a tongue blade. When thrush is scraped, small bleeding points often occur on the underlying mucosa.

34. What is the most common specific etiology diagnosed in patients with systemic febrile illness after international travel?

Malaria, both in children and adults, is the most common etiology. Next in frequency are dengue fever, typhoid fever, rickettsioses, and leptospirosis. Leishmaniasis should also be considered in travelers from endemic areas. Malaria, caused by the protozoan parasite of the genus *Plasmodium,* should be considered in the differential diagnosis in anyone with fever who has traveled to an endemic area in the previous year. More than half of the world's population lives in areas where malaria is endemic. Although there are more than 100 *Plasmodium* species, human infection is caused primarily by five: *P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi. P. falciparum* is responsible for the majority of malarial deaths globally.

Scaggs Huang FA, Schlaudecker E. Fever in the returning traveler. *Infect Dis Clin North Am.* 2018;32(1):163–188.

Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travellers. *N Engl J Med.* 2006;354(2):119–130.

35. What is the classic triad of malaria?

Spiking fevers, anemia, and splenomegaly. Malaria is caused by species of *Plasmodium* (transmitted by the *Anopheles* mosquito), which infect red blood cells (RBCs); certain species (particularly *P. vivax* and *P. ovale)* can have a dormant liver stage. The classic malarial fever involves a periodicity (typically 48 to 72 hours) associated with the rupture of RBCs. Chills, headache, abdominal pain, and myalgias are also common symptoms.

Cavagnaro CS, Brady K, Siegel C. Fever after international travel. *Clin Pediatr Emerg Med.* 2008;9:250–257.

36. How is malaria diagnosed?

Thick and thin blood smears. Thick smears are made by applying the blood film twice to a slide (and incorporating more RBCs). Giemsa stain is applied to both with an attempt to identify parasites in the cells. The thick smear is better for determining the presence of parasites, and the thin smear is better for species identification from the presence of specific cytologic characteristics (Fig. 10.3). A determination of parasite density (a rough gauge to severity of infection) can be made. Therapy depends on the species identified. If smears are negative and clinical suspicion remains strong, repeat smears should be obtained sequentially over a 3-day period; effort should be made to collect specimens when the patient is febrile and parasitemia is heaviest.

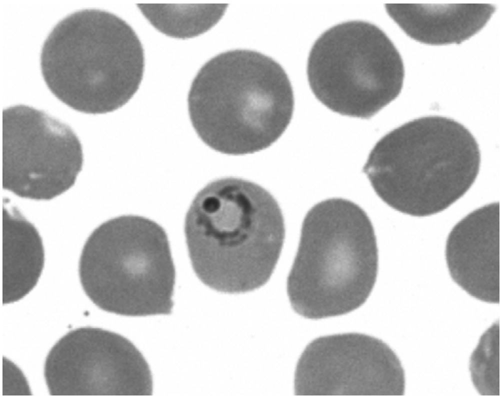

Fig. 10.3 *Plasmodium malariae,* peripheral blood smear. The smear shows a red cell containing a *P. malariae* ring-form trophozoite with one chromatin dot. The cytoplasm ring is thicker than that of *P. falciparum,* which also typically has two chromatin dots. (From Morgan EA. Malaria. In Aster JC, Pozdnyakova O, Kutok JL, eds. *Hematopathology: A Volume in the High Yield Pathology Series,* vol 33. Philadelphia, PA: Elsevier, 2013:43.)

37. Which illness is associated with the term "breakbone fever"?

Dengue fever. The term refers to the classic presentation of fever, severe headache, retro-orbital pain, fatigue, and severe myalgias or arthralgias. Most cases are less severe. The illness is caused by an arbovirus, transmitted by mosquitoes, that is endemic to tropical areas worldwide, including the Caribbean and Central and South America. Leukopenia, thrombocytopenia, and mild elevations of hepatic transaminases are common. Children, more commonly than adults, may develop *dengue hemorrhagic fever,* which encompasses fever, epistaxis, mucosal bleeding, and platelet counts $<100{,}000/\mu L$. This may progress to *dengue shock syndrome* with significant mortality.

38. What causes leptospirosis?

Spirochetes of the genus *Leptospira* cause leptospirosis. These are typically acquired from animal contact or water or soil contaminated by the urine of dogs, rats, or livestock in the course of recreation or work. Acquisition of illness is more common after heavy rainfall or flooding. The incubation period can be up to 1 month. In 90% of cases, the disease is self-limited.

39. What are the phases of leptospirosis?

- **Septicemic phase:** Initially, there are nonspecific symptoms of fever, chills, headache, and a transient rash. Conjunctivitis without purulent discharge occurs in about one-third of cases. Eighty percent of cases feature severe myalgias of the calves and lumbar area. Symptoms may last up to 1 week and improve for 1 to 4 days, when the second phase occurs.
- **Immune-mediated:** Fever returns, accompanied by potentially more severe findings, including aseptic meningitis and Weil syndrome (jaundice, nonoliguric renal failure, hemorrhage due to thrombocytopenia). Severe pulmonary hemorrhages with hemoptysis may develop. The protean manifestations are due to a generalized vasculitis.

American Academy of Pediatrics. Leptospirosis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:508–511.

40. Which organisms are particularly dangerous to clinical microbiology laboratory workers?

The laboratory should be alerted when highly transmissible bacterial agents are suspected in specimens that have been submitted for culture. These bacteria include *Francisella tularensis* (the causative agent of tularemia), *Bacillus anthracis* (anthrax), *Coxiella burnetii* (Q fever), *Leptospira* (leptospirosis), and *Brucella* spp. (brucellosis). In addition, the laboratory should process fungal cultures that contain molds and dimorphic fungi (e.g., *Histoplasma*, *Blastomyces*) in a biosafety cabinet to prevent exposure to spores.

CONGENITAL INFECTIONS

41. Which congenital infections cause cerebral calcifications?

Cerebral calcifications are most frequently observed in **congenital *Toxoplasma*** and **cytomegalovirus (CMV)** infections. They are seen occasionally in patients with congenital HSV infection and rarely in patients with congenital rubella infection or congenital varicella. The calcifications seen in CMV infections are typically found in the periventricular region (Fig. 10.4) because CMV has a predilection for the germinal matrix, as opposed to the calcifications of *Toxoplasma,* which are more generally seen in the brain parenchyma.

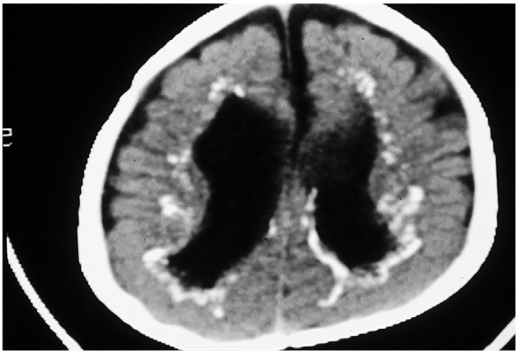

Fig. 10.4 CT scan of infant with congenital CMV infection with periventricular calcification, hydrocephalus, and cerebral atrophy. (From Shakoor A, Sy A, Acharya N. Ocular manifestations of intrauterine infections. In *Pediatric Ophthalmology and Strabismus.* 4th ed. Philadelphia, PA: Elsevier; 2013:81.)

42. What are the late sequelae of congenital infections?

The late sequelae of chronic intrauterine infections are relatively common and may occur in infants who are asymptomatic at birth. Most sequelae present symptoms later in childhood rather than infancy.

- *CMV*: hearing loss, minimal to severe brain dysfunction; motor, learning, language, and behavioral disorders. Longitudinal data from the National Health and Nutrition Examination Surveys (NHANES) have also implicated CMV as a risk factor for cardiovascular disease.

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- *Rubella*: hearing loss, minimal to severe brain dysfunction (motor, learning, language, and behavioral disorders), autism, juvenile diabetes, thyroid dysfunction, precocious puberty, progressive degenerative brain disorder
- *Toxoplasmosis*: chorioretinitis, hydrocephalus, minimal to severe brain dysfunction, hearing loss
- *Neonatal herpes*: recurrent eye and skin infection, minimal to severe brain dysfunction
- *Hepatitis B virus*: chronic subclinical hepatitis, rarely fulminant hepatitis

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Maldonado A, Nizet V, Klein J, et al. Current concepts of infections of the fetus and newborn infant. In Remington J, Klein J, Wilson C, Baker C, eds. *Infectious Diseases of the Fetus and Newborn Infant.* 7th ed. Philadelphia, PA: Elsevier Saunders; 2011:2–23.
Plotkin SA, Alpert G. A practical guide to the diagnosis of congenital infections in the newborn infant. *Pediatr Clin North Am.* 1986;33(3):465–479.

43. What is the most common congenital infection?

Congenital CMV infection is the most common of the so-called congenital TORCH infections (**t**oxoplasmosis, **o**ther (e.g., syphilis), **r**ubella, **c**ytomegalovirus, **h**erpes simplex virus). In some large screening studies, CMV infection occurs in up to 1.3% of newborns. However, the majority (80% to 90%) of infected neonates are asymptomatic at birth or in early infancy.

44. How common is hearing loss from congenital CMV?

It is estimated that one-third to two-thirds of children with symptomatic congenital CMV infection and 7% to 15% of asymptomatic newborns with CMV will develop hearing loss at a median age of 3.5 years. There is debate regarding possible universal screening for newborn CMV infection, especially if the initiation of antiviral therapy could prevent or limit hearing loss. Postnatal exposure to CMV is not associated with hearing loss.

Goderis J, De Leenheer E, Smets K, et al. Hearing loss and congenital CMV infection: a systematic review. *Pediatrics.* 2014;134(5):972–982.
Johnson J, Anderson B. Screening, prevention, and treatment of congenital cytomegalovirus. *Obstet Gynecol Clin North Am.* 2014;41(4):593–599.

45. How is CMV transmitted from mother to infant?

CMV can be transmitted by the transplacental route and through contact with cervical secretions or breast milk. On occasion, transmission may occur by contact with saliva or urine.

46. How should congenital CMV be treated?

The goals of treatment for congenital CMV are to prevent the late sequelae of the disease, primarily sensorineural hearing loss and neurodevelopmental delays. Symptomatic infants (small for gestational age, microcephaly, jaundice, petechiae, hepatosplenomegaly, etc.) should be treated with valganciclovir for 6 months if treatment is started within the first month of life. Asymptomatic infants should not receive therapy, and there remains equipoise about treating infants who are mildly symptomatic (isolated symptoms or only hearing loss at birth).

American Academy of Pediatrics. Cytomegalovirus. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:314–315.

47. What is the risk to the fetus if the mother is infected with parvovirus B19 during pregnancy?

Approximately 30% to 50% of pregnant women are susceptible to parvovirus infection. The risk for fetal loss after seroconversion is 5% to 10% and is greatest when maternal infection occurs during the first half of pregnancy. Fetal loss occurs as a consequence of hydrops, which develops as a result of parvovirus-induced anemia. The signs of parvovirus infection in adults are not very distinctive but may include fever; a maculopapular or lacelike rash, especially in a stocking–glove pattern; and joint pain. There are case reports of aplastic anemia persisting for weeks in surviving neonates.

48. What are the consequences of primary varicella infection during the first trimester?

The *congenital varicella syndrome* consists of a constellation of features:

- Limb atrophy, usually associated with a cicatricial (scarring) lesion
- Neurologic and sensory defects
- Eye abnormalities (chorioretinitis, cataracts, microphthalmia, Horner syndrome)
- Cortical atrophy and developmental disability

This syndrome usually follows maternal infection during the first trimester, although it may be seen after infection up to 20 weeks into gestation.

49. What are the indications for postexposure prophylaxis for varicella in the newborn?

Prophylaxis should be given as soon as possible to a newborn whose mother develops varicella from 5 days before to 2 days after delivery. During this period of high risk, the fetus is exposed to high circulating titers of the virus without the benefit of maternal antibody synthesis. Currently, VariZIG is the purified human immune globulin preparation licensed and available for use in the United States. It is most ideally given within 96 hours (4 days) for greatest effectiveness, but can be given up to 10 days after exposure. Other indications for use in the newborn include the following:

- Premature infants ≥28 weeks of gestation who are exposed in the neonatal period and the mother has no history of chickenpox or positive varicella serology
- Premature infants ≤28 weeks of gestation or whose weight is 1000 g or less and who are exposed in the neonatal period, regardless of maternal history, because little maternal antibody crosses the placenta before the third trimester of pregnancy

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Centers for Disease Control and Prevention. Updated recommendations for use of VariZIG—United States, 2013. *Morb Mortal Wkly Rep.* 2013;62(28):574–576.

50. Does urogenital mycoplasma have a role in neonatal disease?

Ureaplasma urealyticum has been associated with low birth weight and bronchopulmonary dysplasia. This organism has been recovered from neonates with respiratory distress, pneumonia, and meningitis, but a causative role in these diseases has not been proven. Several reports of apparent *Mycoplasma hominis* meningitis and eye infection have been published.

Vertical transmission occurs in up to 60% of newborns whose mothers have positive cultures for these organisms. Risk for transmission is higher in preterm and low-birth-weight infants and correlates with the prolonged rupture of membranes and maternal fever. Infants delivered by cesarean section over intact membranes have a very low rate of colonization compared with infants delivered vaginally.

51. What are the features of congenital rubella syndrome (CRS)?

The most characteristic features of CRS are **congenital heart disease**, **cataracts**, **microphthalmia**, **corneal opacities**, **glaucoma**, and **radiolucent bone lesions**. The features of CRS can be divided into three broad categories:

- *Transient*: Low birth weight, hepatosplenomegaly, thrombocytopenia, hepatitis, pneumonitis, and radiolucent bone lesions
- *Permanent*: Deafness, cataracts, and congenital heart lesions (patent ductus arteriosus > pulmonary artery stenosis > aortic stenosis > ventricular septal defects)
- *Developmental*: Psychomotor delay, behavioral disorders, and endocrine dysfunction

Indigenous rubella transmission and CRS were declared eliminated in the United States in 2004 as a result of universal screening and vaccination policies in pregnant women. However, worldwide CRS remains a major health issue.

52. Should all pregnant women be screened for HSV infection during pregnancy?

Existing data indicate that antepartum cultures of the maternal genital tract fail to predict viral shedding at the time of delivery. Thus **routine** antepartum cultures are **not** currently recommended. However, surveillance data have shown a decline in the overall seroprevalence of HSV in women of childbearing age from 2005 to 2010 compared with 2001 to 2004. About one-fifth to one-third of women of childbearing age are seronegative for HSV-1 and HSV-2. This is in part driven by a significant reduction in the seroprevalence of HSV-1 in young people ages 14 to 19. Concern has been raised that this may lead to an increased incidence of primary HSV infection during pregnancy. Recent algorithms have been developed that incorporate maternal serologic status into the diagnosis and treatment strategies of infants born to mothers with active HSV lesions. Consequently, routine serologic screening (HSV-1 and HSV-2, immunoglobulin G [IgG], and immunoglobulin M [IgM]) may be incorporated into antepartum screening in the future.

Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999-2010. *J Infect Dis.* 2014;209(3):325–333.

Kimberlin DW. The Scarlet H. *J Infect Dis.* 2014;209(3):315–317.

Kimberlin D, Baley J; Committee on Infectious Diseases; Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics.* 2013;131(2):e635–e646.

53. What are risk factors for the development of neonatal HSV disease?

HSV infection of the neonate infant may be acquired *before* delivery (in utero), *during* delivery (intrapartum or perinatal), and *after* delivery (postpartum or postnatal). The majority of illness, approximately 85%, is acquired during the intrapartum period. Classic risk factors for intrapartum or perinatal transmission include:

- Primary, rather than recurrent, maternal infection, especially if acquisition is in the third trimester. (Women with primary genital HSV infections who are shedding HSV at delivery are 10 to 30 times more likely to transmit the virus than women with a recurrent infection.)
- Negative maternal HSV IgG antibody status.
- Prolonged rupture of membranes.
- Violation of mucocutaneous barriers (e.g., use of fetal scalp electrodes).
- Vaginal rather than cesarean delivery.

Stephenson-Famy A, Gardella C. Herpes simplex virus infection during pregnancy. *Obstet Gynecol Clin North Am.* 2014;41(4):601–614.

Kimberlin D, Baley J; Committee on Infectious Diseases; Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics.* 2013;131(2):e635–e646.

Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med.* 2009;361(14):1376–1385.

54. What are the three forms of neonatal HSV disease?

- **Mucocutaneous disease** (localized to the skin, eye, or mouth [SEM])
- **Central nervous system** (CNS) disease
- **Disseminated disease**; multiple organ systems are involved and the clinical syndrome resembles bacterial sepsis

Up to 50% of infants will have CNS complications from either primary CNS disease or disseminated disease with CNS involvement. It is important to note that infants with CNS or disseminated disease may not have visible skin lesions.

55. When should HSV disease be suspected in newborns or infants?

Current recommendations distinguish neonatal HSV *infection,* which is the asymptomatic period when viral replication is occurring, from HSV *disease,* when clinical signs and symptoms of HSV are present. In full-term infants $<$4 weeks and premature infants ($<$32 weeks of gestation) $<$8 weeks, HSV disease should be considered in the following cases:

- **Skin lesions** suspicious for HSV on the infant (may be single or grouped vesicles, pustules, bullae, or denuded skin)
- **Ill-appearing infant** with findings of poor feeding, irritability, lethargy, vomiting, and hypothermia or hyperthermia
- **Seizures or encephalopathy** associated with the current illness
- **Abnormal liver function tests** (elevated alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST])
- **Sterile CSF pleocytosis**

In general, infants with SEM and disseminated disease present with clinical symptoms 10 to 14 days after infection and those with CNS disease 17 to 19 days after infection.

Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus infections. *Semin Perinatol.* 2018;42(3):168–175.

Kimberlin D, Baley J; Committee on Infectious Diseases; Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics.* 2013;131(2):e635–e646.

56. How should the neonate with suspected HSV disease be treated?

Progression from infection to disease is considered inevitable. One of the goals of therapy is to accurately identify infants with infection and intervene to prevent progression to disease. Intravenous acyclovir is the preferred drug and is administered pending definitive diagnosis. For confirmed mucocutaneous disease, treatment is continued for 14 days. For encephalitis and disseminated disease, treatment is continued for 21 days. For infants who have been recognized as having a high risk for progression to disease (e.g., infants born to mothers with primary HSV), 10 days of therapy with intravenous (IV) acyclovir is recommended even if cultures or polymerase chain reaction (PCR) testing of the infant is negative for HSV.

Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus infections. *Semin Perinatol.* 2018;42(3):168–175.

Kimberlin D, Baley J; Committee on Infectious Diseases; Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics.* 2013;131(2):e635–e646.

57. In which groups of women is prenatal hepatitis B surface antigen (HBsAg) screening recommended?

In the past, women were screened for HBsAg if they fell into a high-risk group based on ethnic origin; immunization status; or history of exposure to blood products, IV drugs, or a high-risk partner. However, historic information revealed that, at most, 60% of HBsAg carriers were captured using these screening criteria. Thus it is recommended that **all** pregnant women be screened for HBsAg.

58. What is the risk to the fetus if the mother is infected with hepatitis B virus?

Very significant. Ten percent to 20% of women who are HBsAg positive and 90% of women who are *both* HBsAg positive and seropositive for hepatitis B e antigen (HBeAg) will transmit the virus to their infants in the absence of hepatitis B vaccine at birth. Of women who are acutely infected during pregnancy, the risk for neonatal infection is greatest when maternal infection occurs during the third trimester; up to 90% of these neonates will be seropositive for HBsAg. Chronic hepatitis B virus infection with persistence of HBsAg occurs in 85% to 95% of infants who are infected by perinatal transmission, with a 25% to 30% lifetime prevalence of severe liver disease or liver cancer.

59. How should infants born to mothers with hepatitis B infection be managed?

For infants of any birth weight born to women who are HBsAg positive, hepatitis B immunoglobulin (0.5 mL intramuscularly) and the first dose of hepatitis B vaccine should be administered within 12 hours of delivery to reduce the risk for infection. Although breast milk is theoretically capable of transmitting the hepatitis B virus, the risk for transmission in HBsAg-positive mothers whose infants have received timely hepatitis B immunoglobulin and hepatitis B vaccine is not increased by breastfeeding.

American Academy of Pediatrics. Hepatitis B. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:420.

60. How should infants born to mothers with hepatitis A infection be managed?

Neonates born to mothers with active hepatitis A infection are unlikely to contract the virus, and efficacy of postnatal prophylaxis with hepatitis A immunoglobulin has not been proven. Some experts recommend immunoglobulin if the mother's symptoms begin within 2 weeks before or 1 week after delivery, but this is controversial.

American Academy of Pediatrics. Hepatitis A. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:399.

61. How should infants born to mothers with hepatitis C infection be managed?

The risk for vertical transmission of hepatitis C virus (HCV) is about 6% in mothers who demonstrate the presence of HCV RNA in the blood. This risk is increased in mothers who are coinfected with HIV. No preventive therapy exists. Nucleic amplification testing can be done at 1 to 2 months of age, if desired, to assess for neonatal infection and if negative antibody testing should be performed after 18 months of age. Antibody testing should not be done until after 18 months because that is the expected duration of the passively acquired maternal antibody in infants. Mothers with hepatitis C infection should be advised that transmission of hepatitis C by breastfeeding has not been documented. Accordingly, maternal hepatitis C infection is not a contraindication to breastfeeding, although mothers with cracked or bleeding nipples should consider abstaining.

American Academy of Pediatrics. Hepatitis C. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:430–431.

Wen JW, Haber BA. Maternal-fetal transmission of hepatitis C infection: what is so special about babies? *J Pediatr Gastroenterol Nutr.* 2014;58(3):378–382.

62. How do the clinical features of early and late congenital syphilis differ?

The manifestations of congenital syphilis are variable and may be divided into early and late findings. Early manifestations occur during the first 2 years of life (e.g., "snuffles"); late manifestations, such as peg-shaped or notched central incisors, so-called "Hutchinson teeth," occur after 2 years of age (Fig. 10.5 and Table 10.2).

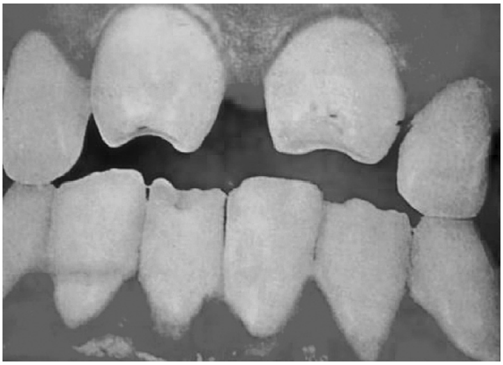

Fig. 10.5 Hutchinson teeth. Note the notched, peg-shaped incisors with enamel defects and incipient caries. (From Rodriguez-Cerdeira C, Silami-Lopes VC. Congenital syphilis in the 21st century. *Actas Dermo-Sifiliográficas (English Edition).* 2011;103:687.)

63. How is the diagnosis of congenital syphilis made?

- All pregnant women and infants should be screened for possible infection with a nontreponemal test for *T. pallidum*. Such tests include the rapid plasma reagin card test (RPR) and the Venereal Disease Research Laboratory (VDRL) slide test.
- If blood from the mother or infant yields a positive nontreponemal serologic test, a specific treponemal test should be performed on the infant's blood. Examples include the fluorescent treponemal antibody (FTA) absorption test and the microhemagglutination test for *T. pallidum*.
- Evaluation of infants with suspected congenital syphilis should also include a complete blood count, analysis of the CSF (including a CSF VDRL), and long-bone radiographs (unless the diagnosis has otherwise been established) to look for characteristic findings (Fig. 10.6).

64. What are the pitfalls of RPR and VDRL testing?

- Nontreponemal tests detect antibodies to cardiolipin and may yield false-positive results in a variety of maternal conditions, such as systemic lupus erythematosus.

Table 10.2 Early and Late Manifestations of Congenital Syphilis

EARLY CONGENITAL SYPHILIS (310 PATIENTS)		LATE CONGENITAL SYPHILIS (271 PATIENTS)	
Hepatomegaly	32%	Pseudoparalysis of Parrot	87%
Skeletal abnormalities	29%	Short maxilla	84%
Splenomegaly	18%	High palatal arch	76%
Birth weight <2500 g	16%	Hutchinson triad	75%
Pneumonia	16%	Saddle nose	73%
Severe anemia, hydrops, edema	16%	Mulberry molars	65%
Skin lesions	15%	Hutchinson teeth	63%
Hyperbilirubinemia	13%	Higoumenakis sign	39%
Snuffles, nasal discharge	9%	Relative protuberance of mandible	26%
Painful limbs	7%	Interstitial keratitis	9%
Cerebrospinal fluid abnormalities	7%	Rhagades	7%
Pancreatitis	5%	Saber shin	4%
Nephritis	4%	Eighth nerve deafness	3%
Failure to thrive	3%	Scaphoid scapulae	0.70%
Testicular mass	0.30%	Clutton joint	0.30%
Chorioretinitis	0.30%		
Hypoglobulinemia	0.30%		

Adapted from Sanchez PJ, Gutman LT. Syphilis. In Feigin RD, Cherry JE, Demmler GJ, Kaplan SL, eds. *Pediatric Infectious Diseases*. 5th ed. Philadelphia, PA: W.B. Saunders; 2004:1730–1732.

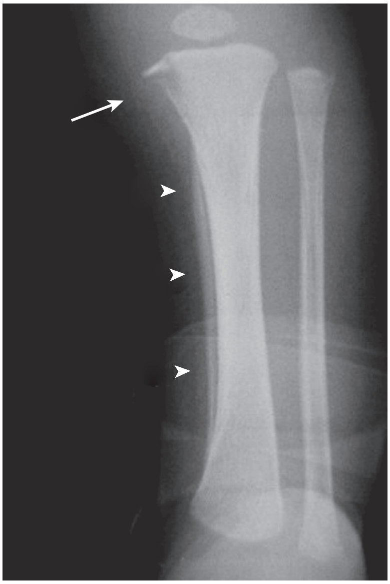

Fig. 10.6 Radiograph of an infant with congenital syphilis shows periosteal reaction along the shaft of the left tibia *(arrowhead)* and a characteristic lucency of the medial proximal tibial metaphysis *(arrow)* called the Wimberger sign, which represents localized bony destruction. (From Donnelly LF. *Pediatric Imaging: The Fundamentals.* Philadelphia, PA: Saunders; 2009:171.)

- False-negative tests may occur because of high titers of antibodies; this is termed the “prozone effect.” It is recommended that the sample be diluted before testing to avoid this.
- A reactive serologic titer may persist after the initial decline (usually four fold) in response to treatment. This low-level titer is usually <1:8 and may persist for life; this so-called “serofast” state can make interpretation of nontreponemal tests difficult.
- A mother who has been treated adequately for syphilis during pregnancy can still passively transfer antibodies to the neonate, which results in a positive titer in the infant in the absence of infection. In this circumstance, the infant’s titer is usually less than the mother’s and reverts to negative over several months.

65. If a pregnant woman is found to have *Chlamydia trachomatis* in her birth canal, what is the most appropriate course of action?

The U.S. Preventative Task Force recommends that all pregnant women <25 years of age or those with high-risk behavior patterns be screened for *C. trachomatis*. Pregnant women with a known chlamydial infection should be treated with oral azithromycin to reduce the risk for neonatal chlamydial pneumonia and conjunctivitis, because untreated mothers may transmit *Chlamydia* to babies born vaginally about 50% of the time. Simultaneous treatment of the male partners with doxycycline or azithromycin should also be undertaken.

U.S. Preventative Task Force. USPSTF Recommendations for STI Screening. www.uspreventiveservicetaskforce. Accessed January 24, 2020.

66. Should newborns of mothers with untreated chlamydial infection receive prophylactic antibiotic therapy?

Although these infants are at increased risk for infection, the efficacy of prophylactic antibiotics is not known and treatment is not indicated. Infants born to women with an untreated chlamydial infection should be followed carefully for signs of conjunctivitis or pneumonia and treated if they are symptomatic.

American Academy of Pediatrics. *Chlamydia trachomatis*. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:280–281.

67. What is the risk to a fetus after primary maternal *Toxoplasma* infection?

The risk depends on the time during pregnancy that the mother becomes infected. Assuming that the mother is untreated, first-trimester infection is associated with a fetal infection rate of about 25%, second-trimester infection with a rate of more than 50%, and third-trimester infection with a rate of roughly 70%. The severity of clinical disease in congenitally infected infants is inversely related to gestational age at the time of primary maternal infection.

68. What is the typical presentation of congenital toxoplasmosis?

At birth, 70% to 90% are asymptomatic. As with other congenital infections, the symptomatic neonatal presentations are varied, ranging from severe disease with hepatosplenomegaly, chorioretinitis, and/or neurologic features (e.g., seizures, hydrocephalus, microcephaly) in about 10% of infected infants to an asymptomatic infection. Among clinically asymptomatic infants, findings such as intracranial calcifications or retinal cysts/scars (Fig. 10.7) may be present, and long-term risks include impaired vision, learning disabilities, and seizures.

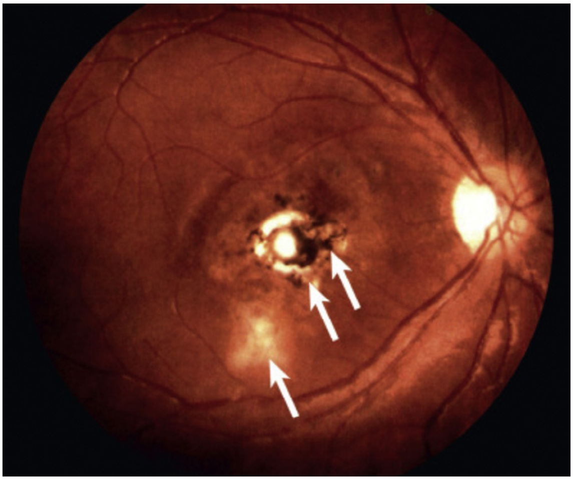

Fig. 10.7 Chorioretinitis caused by congenital toxoplasmosis in a 12-year-old. An active lesion *(single arrow)* is a satellite of an older chorioretinal scar *(double arrows)*. (From Cherry JD, Harrison GJ, Kaplan SL, et al, eds. *Feigin and Cherry’s Textbook of Pediatric Infectious Diseases.* 8th ed. Philadelphia, PA: Elsevier; 2019:221

69. How can a woman minimize the chance of acquiring a *Toxoplasma* infection during pregnancy?

Measures relate to personal hygiene, food preparation, and exposure to cats.

- Avoid raw meat. Using a food thermometer for confirmation, cook whole cuts of meat (excluding poultry) to at least 145°F (63°C), cook ground meat to at least 160°F (71°C), and cook all poultry to at least 165°F (74°C).
- Wash fruits and vegetables before consumption.
- Wash hands and kitchen surfaces thoroughly after contact with raw meat and unwashed fruits or vegetables, and wash thoroughly after gardening.
- Avoid changing cat litter boxes, or wear gloves while changing the litter and wash hands thoroughly afterwards. Changing the litter every 1 to 2 days will also reduce risk.
- Avoid untreated water in high-risk areas, such as developing countries.

EMERGING INFECTIOUS DISEASES

70. Which mycobacterium may infect someone who has a home aquarium?

Mycobacterium marinum. This atypical mycobacterial infection usually begins with clusters of superficial nodules or papules, which can become fluctuant. The condition can be misdiagnosed as a cellulitis. A detailed history can help establish the diagnosis.

71. What are possible sources for an anthrax infection in a 17-year-old who lives on a cattle farm, makes and plays drums as a hobby, and works in a microbiology laboratory after school?

- **Cutaneous anthrax** is the most common form of anthrax. It occurs when spores invade a violation in local skin integrity. Infection usually develops from 1 to 7 days after exposure. Without treatment, cutaneous anthrax is fatal 20% of the time, but it is curable with therapy. Cutaneous anthrax has been called "wool sorters disease," because the spores are found in animal hides (as well as other raw animal products), such as those used in wool processing or in making traditional hide drums. It can be contracted through improper handling of laboratory specimens. It was used as an agent of bioterror in the United States in 2001.
- **Inhalation anthrax** occurs when the spores are inhaled. Dissemination then occurs through lymphatic spread. Infection usually develops 7 to 14 days after exposure but may occur up to 60 days after exposure. Survival with treatment is ≈55%.
- **GI** anthrax occurs when spores are ingested, typically through raw or undercooked meat. Infection usually develops from 1 to 7 days after exposure. Survival with treatment is ≈60%.

Our patient could have contracted any form of the disease from a variety of his exposures. As with many infectious diseases, a careful history will often reveal the source of the infection.

72. What are the novel coronaviruses?

Coronaviruses are named for the crownlike spikes on their surface; they typically cause respiratory disease on the spectrum of the common cold, but three novel coronaviruses have been implicated in severe and sometimes fatal respiratory disease:

- **Severe acute respiratory syndrome (SARS)**, termed *SARS-CoV,* was first recognized in China in 2002. It spread to multiple countries and caused several hundred deaths from 2002 to 2003. The virus is felt to have originated in wild animals (civet cats and bats have been implicated) with transmission to humans who contacted them in markets in urban areas.
- **Middle East respiratory syndrome (MERS)**, termed *MERS-CoV,* was first recognized in Saudi Arabia in 2012. All cases to date have been linked to countries in and near the Arabian Peninsula. The disease is thought to have a natural reservoir in camels.
- **COVID-19**, the official WHO designation for coronavirus disease identified in late 2019, is a novel coronavirus (SARS-CoV-2) which originally caused clusters of pneumonia in Wuhan, China. The virus is similar to two bat coronaviruses, which may have been the primary source. Epidemiologic data, particularly among children, are evolving, but the virus spread rapidly among humans on multiple continents and was declared a pandemic by the WHO in March 2020.

73. What viral etiology should be considered in a patient with acute, unexplained respiratory illness who is not febrile?

Enterovirus D68 (EV-D68). This is a nonpolio enterovirus first described in California in 1968. Symptoms range from mild respiratory illness with rhinorrhea, sneezing, cough, and myalgia to severe symptoms such as wheezing, hypoxia, and acute respiratory distress syndrome. However, even patients with serious illness due to EV-D68 may not have fever. Additionally, EV-D68 has been associated (although not causally substantiated) in a cluster of cases of *acute limb weakness* that have occurred every 2 years in the United States since 2014. Most patients were found to have a distinctive pattern of abnormalities of the gray matter of the spinal cord on magnetic resonance imaging (MRI).

Holm-Hansen CC, Midgley SE, Fischer TK. Global emergence of enterovirus D68: a systematic review. *Lancet Infect Dis.* 2016;16(5):e64–e75.

Foster CB, Friedman N, Carl J, et al. Enterovirus D68: a clinically important respiratory enterovirus. *Cleve Clin J Med.* 2015;82(1):26–31.

74. What two diseases in particular should be in the differential diagnosis for a traveler returning from the Caribbean with a fever and rash?

Dengue fever and **Chikungunya virus infection.** Dengue and Chikungunya viruses are both transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquitoes and have overlapping clinical features and similar endemicity. **Dengue** has three clinical syndromes:

- *Undifferentiated fever* presents as a general febrile illness with fever, malaise, and other mild symptoms that overlap with a number of other viral syndromes. This is a typical presentation in children with their first infection.
- *Dengue fever with or without hemorrhage* presents with 2 to 7 days of high fever and $\geq$2 other symptoms such as severe headache, retro-orbital eye pain, myalgias, arthralgias, maculopapular rash, or petechial rash.
- *Dengue hemorrhagic fever or Dengue shock syndrome* presents initially as Dengue fever but progresses to plasma leak and disseminated intravascular coagulation.

Dengue fever or hemorrhagic fever usually occurs in older children or adolescents who have had a previous infection.

Chikungunya infection is characterized by acute onset of fever $>$102°F ($>$39°C) and joint pain that is usually severe, bilateral, and symmetric, as well as headache, myalgia, arthritis, nausea/vomiting, and a maculopapular rash, similar to dengue fever.

Real-time PCR diagnosis is available for both dengue and Chikungunya through the CDC and may be performed within 5 days of onset of symptoms. After that time frame, IgG and IgM serologic testing should be performed.

75. What is the most common viral intestinal infection you can get from eating at a salad bar?

Noroviruses are estimated to be responsible for up to 50% of foodborne outbreaks of viral gastroenteritis. Additionally, the majority ($>$90%) of diarrheal disease outbreaks on cruise ships are caused by noroviruses. The source of these outbreaks often stems from unsafe food-handling practices from infected food service workers. Foods such as raw fruits and leafy green vegetables are often involved. Nausea, vomiting, and watery diarrhea with abdominal cramping have an acute onset 12 to 48 hours after exposure and resolve without treatment 24 to 72 hours later.

76. When was the Ebola virus first discovered?

1976. There were two simultaneous outbreaks, one in Sudan and one in the Republic of Congo. The name derives from a village in the Congo near the Ebola River where the outbreak occurred.

77. What are the clinical features of an Ebola infection?

After an incubation period of 2 to 21 days, clinical disease begins with nonspecific signs and symptoms, including fever, headache, myalgia, abdominal pain, and malaise, which overlap with many other viral and parasitic diseases in endemic regions. This is then followed several days later by vomiting and diarrhea. Conjunctival injection or subconjunctival hemorrhage, hepatic dysfunction (AST $>$ ALT), and metabolic derangements also are common at this stage. In the most severe cases, microvascular instability and subsequent hemorrhage, most commonly from the GI tract, will occur. CNS manifestations can occur but are less common in children than in adults. Accompanying respiratory symptoms are more common in children. Mortality is high ($\approx$50% to 70%), but this is likely confounded by low-resource setting, age, baseline health, and comorbid conditions.

78. What is the natural reservoir host of the Ebola virus?

Although the reservoir remains unknown, many researchers believe the virus is animal-borne initially, and **fruit bats** are the most likely natural reservoir. Primates (apes and monkeys) are also possibilities. Humans may contract the disease from exposure to infected bat excreta or saliva or by exposure to blood and bodily fluids from other infected sources, such as nonhuman primates that are consumed as food. Once the first human becomes infected through contact with an infected animal, person-to-person transmission (as well as spillover from continued contact with an animal reservoir or surface and material contaminated with infected fluids) allows an epidemic to promulgate.

FEBRILE CHILD

> *"…since the advent of modern clinical thermometry by Wunderlich in 1871, the ritual of temperature taking has been surpassed only by Alexander Graham Bell's invention in 1874 as the major curse of pediatrics."*
>
> DS Smith. Fever and the pediatrician. *J Pediatr.* 1970;77(5):935.

79. At what temperature does a child have fever?

This is a simple question without a simple answer. Because body temperatures vary among individuals and age groups and vary over the course of the day in a given individual (lowest around 4:00 to 5:00 AM and highest in late afternoon and early evening), a precise cutoff point is difficult to determine. In children between the ages of 2 and 6 years, diurnal variation can range up to 1.6°F (0.9°C). Infants tend to have a higher baseline temperature pattern, with 50% having daily rectal temperatures higher than 100.0°F (37.8°C); after the age of 2 years, this elevated baseline falls. In addition, activity and exercise (within 30 minutes), feeding or meals (within 1 hour), and hot foods (within 1 hour) can cause body temperature elevations. Most authorities agree that for a child $<$3 months, a rectal temperature >100.4°F (38°C) constitutes fever. In infants between the ages of 3 and 24 months (who tend to have a higher baseline), a temperature of ≥101°F (38.3°C) likely constitutes fever. In those >2 years, as the baseline falls, fever more commonly is defined as a rectal temperature >100.4°F (38°C).

80. Where did the popular notion that a normal temperature is 98.6°F originate?

The temperature 98.6°F was established as the mean healthy temperature in 1868 after >1 million temperatures from 25,000 patients were analyzed. Ironically, these were axillary temperatures, and the waters of what constitutes normal have been muddied since.

Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6°F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA.* 1992;268(12):1578–1580.

81. How does temperature vary among different body sites?

There can be significant variability in the relationship between different sites, and conversions should be done with caution. As a general guideline:

- **Rectal:** Standard
- **Oral:** 1°F (0.5° to 0.6°C) lower
- **Axillary:** 1.5° to 2.0°F (0.8° to 1.0°C) lower
- **Tympanic:** 1°F (0.5° to 0.6°C) lower

There also is a great deal of variability in cutaneous (such as forehead or temporal artery) infrared thermometry, depending on a variety of conditions, including age.

82. How accurate is parental palpation for fever in infants?

It is common for parents to report a subjective fever by palpation without measuring a temperature by thermometry. Palpation by parents has a sensitivity and specificity of about 80% in children >3 months. In infants <3 months, the positive-predictive value of a parent reporting a palpable fever is about 60%, with a negative-predictive value of 90%. For these younger infants, for whom identification of fever carries potentially greater clinical repercussions, parents seem to overestimate the presence of a fever, but they are more accurate determining when a child is afebrile.

Katz-Sidlow RJ, Rowberry JP, Ho M. Fever determination in young infants: prevalence and accuracy of parental palpation. *Pediatr Emerg Care.* 2009;25(1):12–14.

83. How should the temperature of young infants be taken?

In infants who are <3 months (when fever can be more significant clinically), a **rectal temperature** is the preferred method. Tympanic recordings are much less sensitive in this age group because the narrow, tortuous external canal can collapse, thereby resulting in readings obtained from the cooler canal rather than the warmer tympanic membrane. Cutaneous infrared temporal artery thermometry may have reduced diagnostic accuracy in this age group. Axillary temperatures often underestimate fever. The oral route is typically not used until a child is 5 to 6 years of age.

84. How do environmental factors affect an infant's temperature?

Studies in neonates and infants have found mixed results. One study of newborns in a warm environment of 80°F (26°C) found that rectal temperatures in bundled infants could be elevated to more than 38°C, which is the "febrile range," although newborn infants may have a physiologically lower body temperature. Another study of infants ≤3 months old found that when infants were bundled for up to 65 minutes at room temperatures of 72° to 75°F (22.2° to 23.8°C), it did not result in any rectal temperatures >100.4°F (38°C). Infants are also prone to hypothermia, especially in the hours after birth. Direct skin-to-skin contact in newborn infants has been shown to raise and sustain newborn temperatures. Smaller or preterm infants may be most susceptible to environmental factors such as cooler ambient temperatures.

Nimbalkar SM, Patel VK, Patel DV, et al. Effect of early skin-to-skin contact following normal delivery on incidence of hypothermia in neonates more than 1800 g: randomized control trial. *J Perinatol.* 2014;34(5):364–368.

Grover C, Berkowitz CD, Lewis RJ, et al. The effects of bundling on infant temperature. *Pediatrics.* 1994;94(5):669–673.

85. What is occult bacteremia?

Occult bacteremia refers to the finding of bacteria in the blood of patients, usually between the ages of 3 and 36 months, who are febrile without a clinically apparent focus of infection.

86. How has the pneumococcal vaccine (PCV) affected the incidence of occult bacteremia?

In trials done after the introduction of the *Haemophilus influenzae* type B (Hib) vaccine (1990) but before the introduction of the pneumococcal conjugate vaccine (2000), bacteremia rates for pneumococcus ranged from 1.6% to 3.1% in febrile (≥102.2°F [39°C]), non–toxic-appearing children from ages 2 to 36 months. Since the introduction of the pneumococcal conjugate vaccine against seven serotypes and two cross-reactive serotypes (PCV-7) of *Streptococcus pneumoniae*, bacteremia rates for *S. pneumoniae* have fallen to <1%. This benefit was sustained after the introduction in 2010 of the 13-valent PCV, which added coverage against six other serotypes. Other benefits, such as reduction in all types of invasive pneumococcal disease (e.g., community-acquired pneumonia), have also been noted, especially in children <2 years of age. Children who are incompletely immunized are at higher risk compared with those fully immunized, but this effect is mitigated somewhat by herd immunity in countries and communities with high vaccination rates.

Greenhow TL, Hung YY, Herz AM, et al. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J.* 2014;33(6):595–599.

Joffe MD, Alpern ER. Occult pneumococcal bacteremia: a review. *Pediatr Emerg Care.* 2010;26(6):448–454.

Wilkinson M, Bulloch B, Smith M. Prevalence of occult bacteremia in children ages 3 to 36 months presenting to the emergency department in the postpneumococcal conjugate vaccine era. *Acad Emerg Med.* 2009;16(3):220–225.

87. What is meant by “serotype replacement”?

This is an increase in infections caused by serotypes not included in a vaccine. In the case of the initial conjugate pneumococcal vaccine in 2000, seven vaccine serotypes and two cross-reactive serotypes were included in the vaccine and accounted for about 80% of invasive pneumococcal disease. Pneumococci have >90 serotypes, and after the introduction of that vaccine, there was a rise of infections caused by nonvaccine serotypes, particularly 19A. The 13-valent conjugate vaccine (which added serotype 19A, among others) was licensed in 2010, and reports do indicate new serotype replacement patterns.

Angoulvant F, Levy C, Grimprel E, et al. Early impact of 13-valent pneumococcal conjugate vaccine on community-acquired pneumonia in children. *Clin Infect Dis.* 2014;58(7):918–924.

Muñoz-Almagro C, Jordan I, Gene A, et al. Emergence of invasive pneumococcal disease caused by nonvaccine serotypes in the era of the 7-valent conjugate vaccine. *Clin Infect Dis.* 2008;46(2):183–185.

88. What is the proper way to evaluate and manage febrile illness in neonates ≤ 28 days?

In general, patients <1 month with fever (≥ 100.4°F (38.0°C) warrant urgent evaluation (including blood, urine, and CSF cultures) because of higher rates of bacteremia and meningitis (including pathogens from the neonatal period, such as group B streptococci) and greater difficulty in global assessment of wellness compared with infants >28 days of age.

Powell EC, Mahajan PV, Roosevelt G, et al. Epidemiology of bacteremia in febrile infants aged 60 days and younger. *Ann Emerg Med.* 2018;71(2):211–216.

Jain S, Cheng J, Alpern ER, et al. Management of febrile neonates in US pediatric emergency departments. *Pediatrics.* 2014;133(2):187–195.

89. What are the evaluation and management of febrile illness in infants >28 days to 90 days?

This remains controversial, as the Hib and pneumococcal conjugate vaccines have altered the landscape of invasive bacterial disease. On average, up to 7% of febrile infants who are <3 months have serious bacterial infections (SBIs), which can include bacteremia, meningitis, osteomyelitis, septic arthritis, UTI, or pneumonia. Of these, UTIs comprise the greatest percentage of bacterial infections. The incidence of bacterial meningitis and SBI due to *S. pneumoniae* has fallen; this is likely due in part to herd immunity secondary to vaccination of older infants. Consequently, in a well-appearing febrile infant, a previous emphasis on a comprehensive evaluation (i.e., urine, serum, and CSF testing) has declined significantly. A 2014 study of 37 U.S. pediatric emergency departments found that comprehensive evaluations were done in febrile infants (29 to 56 days) only 49% of the time and in older infants (57 to 89 days) only 13% of the time without a change in outcome compared with those without comprehensive evaluations. Thus local institutional guidelines based on regional epidemiology, institutional experience, provider experience, and cohort data have become the norm in the absence of national guidelines. A urinalysis and urine culture are now the most important laboratory studies given the higher likelihoods of UTIs compared with other occult bacterial processes. Many centers also obtain a complete blood count and blood culture in this age group. Lumbar punctures (LPs) are commonly deferred in a smiling, well-appearing, febrile infant.

Dorney K, Bachur RG. Febrile infant update. *Curr Opin Pediatr.* 2017;29(3):280–285.

Aronson PL, Thurm C, Alpern ER, et al. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. *Pediatrics.* 2014;134:667–677.

90. How should older infants and toddlers (3 to 36 months old) with fever and no apparent source be managed?

Previously, much of the evaluation that centered on febrile children in this age group dealt with identifying possible occult bacteremia with the intent of using empiric antibiotic treatment to lessen the chance of dissemination to focal complications (particularly meningitis). However, rates of bacteremia and meningitis have fallen dramatically, particularly with the introduction of the conjugate pneumococcal vaccine. The most common cause of SBI in children with fever without a source in this age range is an occult UTI. Most pediatric infectious disease experts no longer recommend a complete blood count and/or blood culture or any laboratory tests (other than urinalysis and urine culture in certain settings) in the evaluation of a well-appearing febrile infant >90 days who has received Hib and pneumococcal vaccines because of the low risk for bacteremia and meningitis.

Scarfone R, Murray A, Gala P, Balamuth F. Lumbar puncture for all febrile infants 29-56 days old: a retrospective cohort reassessment study. *J Pediatr.* 2017;187:200–205.

Woll C, Neuman MI, Aronson PL. Management of the febrile young infant: update for the 21st century. *Pediatr Emerg Care.* 2017;33(11):748–753.

Arora R, Mahajan P. Evaluation of child with fever without source: a review of literature and update. *Pediatr Clin North Am.* 2013;60(5):1049–1062.

91. When is a chest radiograph indicated for a febrile young infant?

Although some clinicians believe that chest radiographs should be performed for all febrile infants who are <2 to 3 months, it is probably not necessary. In general it is recommended for neurologically normal infants who have respiratory symptoms or signs, including cough, tachypnea, irregular breathing, retractions, rales, wheezing, or decreased breath sounds. In a study done in the pre-PCV era of infants <8 weeks who were admitted with fever, 31% of patients with respiratory manifestations had an abnormal chest radiograph compared with only 1% of asymptomatic infants. Leukocytosis (>20,000/mL) in febrile (>102.2°F [39°C]) patients <5 years increases the likelihood of an "occult pneumonia." In most cases, it is not possible to differentiate viral from bacterial pneumonias radiologically.

Hernandez DA, Nguyen V. Fever in infants <3 months old: what is the current standard? *Pediatr Emerg Med Rep.* 2011;16:1–15.

Murphy CG, van de Pol AC, Harper MB, et al. Clinical predictors of occult pneumonia in the febrile child. *Acad Emerg Med.* 2007;14(3):243–249.

Crain EF, Bulas D, Bijur PE, Goldman HS. Is a chest radiograph necessary in the evaluation of every febrile infant less than 8 weeks of age? *Pediatrics.* 1991;88(4):821–824.

92. What is the approach for a 2-week-old, otherwise healthy, afebrile, full-term female who presents to the emergency department with mastitis?

As the overall incidence of community-acquired *S. aureus,* including MRSA isolates, increases, management of mastitis is controversial. Case series have shown that the majority of these lesions from which organisms are recovered are "community strains" of *S. aureus.* Included in the differential diagnosis is GBS cellulitis–adenitis syndrome caused by serotype III. SSTIs are commonly treated as serious bacterial infections, but many of these infants are afebrile and without signs of disseminated infection, making their management unclear. Many providers will proceed with a full sepsis evaluation, including LP, because of the age of the infant. As with the febrile infant, there is a diversity of practices both within and among institutions based on local epidemiology, provider experience, and patient demographics. Therapy should include coverage for *S. aureus*, including MRSA. One large case series found that a number of infants with localized *S. aureus* SSTIs who had an LP done had a sterile CSF pleocytosis, hypothesized to be an inflammatory reaction to bacterial toxins, further confounding treatment and diagnosis. GBS cellulitis–adenitis is a manifestation of late-onset GBS disease and should be aggressively evaluated and treated if there is suspicion for this condition.

Nguyen R, Bhat R, Teshome G. Question 2: is a lumbar puncture necessary in an afebrile newborn infant with localised skin and soft tissue infection? *Arch Dis Child.* 2014;99(7):695–698.

Fortunov RM, Hulten KG, Hammerman WA, et al. Evaluation and treatment of community-acquired *Staphylococcus aureus* infections in term and late-preterm previously healthy neonates. *Pediatrics.* 2007;120(5):937–945.

93. What is a CLABSI?

A *central line–associated bloodstream infection* (CLABSI) is defined as a bloodstream infection in a symptomatic patient with a central venous catheter that terminates at or close to the heart and who has had a hospital stay of at least 3 days. The line must be in place for >2 calendar days, and the bloodstream infection (BSI) must occur while the line is in place or within 1 day of removal. It is estimated that most of these infections may be preventable with proper aseptic techniques during insertion and dressing changes, appropriate use of catheters (including site placement), and removal of a catheter when no longer clinically essential.

Hazamy P, Haley VB, Tserenpuntsag B, et al. Effect of 2013 National Healthcare Safety Network definition changes on central line bloodstream infection rates: audit results from the New York State Department of Health. *Am J Infect Control.* 2015;43(3):280–282.

Wylie MC, Graham DA, Potter-Bynoe G, et al. Risk factors for central line-associated bloodstream infection in pediatric intensive care units. *Infect Control Hosp Epidemiol.* 2010;31(10):1049–1056.

94. How long should one wait before a blood culture is designated negative?

Bacterial growth is evident in most cultures of infected blood within 48 hours or earlier. With the use of continuous monitoring techniques, a study at Children's Hospital of Philadelphia of 200 cultures from central venous catheters found that the median time for a positive blood culture was 14 hours. In addition, 99.2% of cultures with gram-negative bacteria were positive by 36 hours, and 97% of cultures with gram-positive bacteria were positive by 36 hours. A 2019 study from England of over 50,000 blood cultures found that 92% of definite pathogens in both neonates and older children were positive by 24 hours. A study from Australia of neonatal blood cultures found that the median time for positivity for GBS was 9 hours, that for *E. coli* was 11 hours, and that for coagulase-negative staphylococci was 29 hours. Although 36 to 48 hours is generally sufficient time to isolate common bacteria present in the bloodstream, fastidious organisms may take longer to grow. Therefore, when one suspects anaerobes, fungi, or other organisms with special growth requirements, a longer time should be allowed before concluding that a culture is negative.

Theodosiou AA, Mashumba F, Flatt A. Excluding clinically significant bacteremia by 24 hours in otherwise well febrile children younger than 16 years. *Pediatr Infect Dis J.* 2019 Sep;38(9):e203–e208.

Shah SS, Downes KJ, Elliot MR, et al. How long does it take to "rule out" bacteremia in children with central venous catheters? *Pediatrics.* 2008;121(1):135–141.

Jardine L, Davies MW, Faoagali J. Incubation time required for neonatal blood cultures to become positive. *J Paediatr Child Health.* 2006;42(12):797–802.

95. What is the utility of so-called "rapid" pathogen testing?

Testing of antigens for influenza A and B and RSV was developed several years ago to provide rapid diagnosis of respiratory viruses known to cause severe disease in certain populations and for which some therapy exists. These generally had good specificity but lower sensitivity. More recently, PCR-based testing has been shown to have a very high sensitivity and specificity for many common viruses and bacteria. These have been combined into panels of common respiratory viruses, pertussis, and bacteria causing atypical pneumonia, as well as a panel of common GI viruses, protozoa, and enteropathic bacteria. On one hand, some believe that the use of these tests may reduce antibiotic use in respiratory viral illnesses; others worry that the diagnosis of a common respiratory virus in a febrile young child may be falsely reassuring. Recommendations developed during the H1N1 influenza epidemic in 2009 discouraged outpatient and emergency department providers from testing patients for influenza who did not meet guidelines for antiviral therapy, but did recommend testing for patients ill enough to be hospitalized, for those with risk factors for severe disease, or patients with a suspected nosocomial illness. Initiation of antiviral therapy should not be delayed pending results of any viral testing in a child in whom treatment is indicated.

96. When is a fever considered a fever of unknown origin (FUO)?

FUO is defined as the presence of daily (or nearly daily) fever (temperature of >101°F [38.3°C]) for at least 8 days in a single illness in a patient for whom a careful history, thorough physical examination, and preliminary laboratory data fail to reveal the probable cause.

97. What is the eventual etiology of fever in children with FUO?

The differential diagnosis is extremely broad. The three major categories are **infectious**, **inflammatory** (e.g., vasculitis, rheumatoid arthritis), and **neoplastic**. Approximately half of cases have no identifiable cause, and the fever resolves without explanation. The largest category is *infectious.* As a general rule, in children <6 years, the most common causes involve respiratory or genitourinary tract infections; localized infections (e.g., abscess, osteomyelitis); juvenile rheumatoid arthritis; and, infrequently, leukemia. Adolescents, on the other hand, are more likely to have tuberculosis; inflammatory bowel disease; another autoimmune process; or, infrequently, lymphoma.

Marshall GS. Prolonged and recurrent fevers in children. *J Infect.* 2014;68(Suppl 1):S83–S93.

Edwards KM, Halasa NB. Fever of unknown origin (FUO) and recurrent fever. In Bergelson JM, Shah SS, Zaoutis TE, eds. *Pediatric Infectious Diseases: The Requisites in Pediatrics*. Philadelphia, PA: Mosby Elsevier; 2008:266–273.

98. How should a child with FUO be evaluated?

FUO is more likely to be an unusual presentation of a common disorder than a common presentation of a rare disorder. The diagnostic approach includes a meticulous fever diary with vigilance for the appearance of new signs and symptoms. A complete and detailed history is key, with particular attention to possible exposures, including animals, unpasteurized milk *(Yersinia* or *Campylobacter)*, uncooked poultry, ticks, pica or dirt ingestion (possible *Toxocara* or *Toxoplasma*), rabbits *(Tularemia)*, mosquitoes, stagnant water, and reptiles *(Salmonella).* Travel history is also important. After performing a thorough physical examination, one should avoid indiscriminately ordering a large battery of tests. Initial tests may include a complete blood count, screen for inflammation (C-reactive protein or erythrocyte sedimentation rate), tests of renal function, liver enzymes, uric acid, lactate dehydrogenase (LDH), urinalysis, urine and blood cultures, tuberculin skin test, and chest radiograph. Laboratory studies should subsequently be targeted as much as possible toward the most likely diagnostic possibilities. The pace of the workup is determined by the severity of the illness.

Antoon JW, Peritz DC, Parsons MR, et al. Etiology and resource use of fever of unknown origin in hospitalized children. *Hosp Pediatr.* 2018;8(3):135–140.

Marshall GS. Prolonged and recurrent fevers in children. *J Infect.* 2014;68(Suppl 1):S83–S93.

Tolan RW Jr. Fever of unknown origin: a diagnostic approach to this vexing problem. *Clin Pediatr.* 2010;49(3):207–213.

99. What is PFAPA?

PFAPA is the acronym for the syndrome of **p**eriodic **f**ever, **a**phthous stomatitis, **p**haryngitis, and cervical **a**denitis, a clinical syndrome of unclear etiology that is responsive to very short courses of corticosteroids, and in some cases, interleukin-1 blockers, for individual episodes. PFAPA is perhaps the most common cause of regular, recurrent fevers in children. It is a benign, self-limited condition that resolves without therapy and typically remits as children grow older. Tonsillectomy provides benefit in protracted cases.

Ali NS, Sartori-Valinotti JC, Bruce AJ. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. *Clin Dermatol.* 2016;34(4):482–486.

Feder HM, Salazar JC. A clinical review of 105 patients with PFAPA (a periodic fever syndrome). *Acta Paediatr.* 2010;99(2):178–184.

100. In addition to PFAPA, which syndromes are associated with periodic fevers?

Predictable periodic fever is a cardinal feature of a small number of *autoinflammatory disorders,* which are thought to be due to primary dysregulation of the innate immune system and may involve mutated proteins. Many are hereditary and have ethnic predilections. Periodic fever is uncommon in infectious diseases and malignancies. The most common periodic fever syndromes are summarized in Table 10.3.

Table 10.3 Characteristics of PFAPA Versus Other Selected Fever Syndromes

	PFAPA	FAMILIAL MEDITERRANEAN FEVER	HYPER-IGD SYNDROME (HIDS)	TNF-RECEPTOR-ASSOCIATED PERIODIC SYNDROME (TRAPS)
Age at onset	Childhood	<10 yr (80%)	Childhood	Variable
Length of fever episode	4 days	2 days	4-6 days	1-3 wk
Interval between fever episodes	2-8 wk	Irregular	Irregular	Irregular
Associated symptoms and signs	Aphthous stomatitis, pharyngitis, adenitis	Painful pleuritis, peritonitis, oligoarthritis, foot and ankle rash	Abdominal pain, cervical adenopathy, splenomegaly	Abdominal pain, pleuritis, rash, myalgias, orbital edema
Inheritance	Random	Autosomal recessive	Autosomal recessive	Autosomal dominant

IgD, Immunoglobulin D; *PFAPA,* syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; *TNF,* tumor necrosis factor.

Data from Goldsmith DP. Periodic fever syndromes. *Pediatr Rev.* 2009;30(5):e34–e41.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

101. How common is the maternal-to-infant transmission of HIV?

Virtually all infants born to mothers who are HIV-1 seropositive will acquire antibody to the virus transplacentally. Without treatment for either the mother or the infant, about 25% (range, 13% to 39%) of these infants will ultimately develop an active HIV infection. With adequate maternal and infant prophylaxis, the perinatal transmission rate is <1%. Breastfeeding has contributed significantly to infection rates in areas of the world where formula is difficult to obtain or local water sources are unreliable. Vertical transmission of HIV-2 is less common, occurring in 0% to 4% of cases.

DeCock KM, Fowler MG, Mercier E, et al. Mother-to-child transmission of HIV-1: timing and implications for prevention. *Lancet Infect Dis.* 2006;11:726–732.
Abrams EJ, Weedon J, Bertolli J, et al. New York City Pediatric Surveillance of Disease Consortium, Centers for Disease Control and Prevention: aging cohort of perinatally human immunodeficiency virus-infected children in New York City. New York City Pediatric Surveillance of Disease Consortium. *Pediatr Infect Dis J.* 2001;20(5):511–517.

102. What drugs are recommended for reducing the maternal-to-infant transmission of HIV?

Currently, interventions to prevent transmission target the late intrauterine and intrapartum periods when the highest likelihood of transmission occurs. HIV-infected pregnant women in the United States are treated with combination antiretroviral therapy in the same manner as nonpregnant adults. All HIV-exposed newborn infants should receive zidovudine (AZT) at gestational age appropriate dosing for the first 4 to 6 weeks of life. Among infants born to mothers with high viral loads or those in whom antepartum and/or intrapartum prophylaxis was incomplete or not received, the addition of prophylactic-dose nevirapine is recommended (first dose at birth to 48 hours, second dose 48 hours after the first dose, and third dose 96 hours after the second dose). Nevirapine should be started as soon as possible after birth. Treatment dosing of AZT, 3TC (lamivudine), and nevirapine can also be given to extremely high-risk infants who are thought to have contracted HIV in utero. Elective cesarean delivery is also recommended for women with high HIV loads.

Fowler MG, Flynn P, Aizire J. What is new in perinatal HIV prevention? *Curr Opin Pediatr.* 2018;30(1):144–151.
AIDS Info: Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. www.aidsinfo.nih.gov. Accessed June 14, 2019.

103. What are the risk factors for perinatal transmission of HIV?

- AZT monotherapy during pregnancy (compared with combination antiretroviral therapy)
- High maternal viral load at or near delivery
- Rupture of membranes >4 hours before delivery
- Fetal instrumentation with scalp electrodes and forceps
- Vaginal delivery (especially with high maternal viral loads)
- Episiotomies and vaginal tears
- Prematurity and low birth weight (possible impaired fetal or placental membranes)
- Concurrent maternal HSV-2 infection (increased shedding of HIV in genital secretions)
- Breastfeeding
- Incidence of HIV during pregnancy and postpartum

ACOG Committee Opinion. Labor and delivery management of women with human immunodeficiency virus infection. *Obstet Gynecol.* 2018;132(3):e131–e137.
Paintsil E, Andiman WA. Update on successes and challenges regarding mother-to-child transmission of HIV. *Curr Opin Pediatr.* 2009;21:95.
Landesman SH, Kalish LA, Burns DN, et al. Obstetrical factors and the transmission of HIV type 1 from mother to child. *N Engl J Med.* 1996;334(25):1617–1623.

104. Should HIV-infected women breastfeed?

No. HIV has been shown to be present in breast milk and also to be transmissible by breastfeeding. Worldwide, up to one-third to one-half of infant transmission of HIV may occur through breastfeeding. This risk is increased when the infection is acquired after birth. Thus, in developed countries where alternative means of nutrition (i.e., formula) are readily available, breastfeeding is not recommended. In developing countries where breastfeeding may be protective against other causes of significant morbidity and mortality (e.g., diarrheal and respiratory illnesses) and alternative means of nutrition are less reliably available, breastfeeding remains the best infant nutritional option. The World Health Organization (WHO) recommends exclusive breastfeeding when replacement feeding is not acceptable, feasible, affordable, or safe. Exclusive breastfeeding appears to have lower rates of transmission than mixed (e.g., formula and solid foods) breastfeeding. It remains unclear what the optimal duration of breastfeeding is to balance its protective effect with the risk for HIV transmission, although abrupt weaning appears to increase infant mortality. Studies continue to document at least some benefit to maternal and/or infant antiretroviral use to prevent transmission during the breastfeeding period.

AIDS Info. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. www.aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf. Accessed June 14, 2019.
Jamieson DJ, Chasela CS, Hudgens MG, et al. Maternal and infant antiretroviral regimens to prevent postnatal HIV-1 transmission: 48-week follow-up of the BAN randomised controlled trial. *Lancet.* 2012;379(9835):2449–2458.
Kuhn L, Reitz C, Abrams EJ. Breastfeeding and AIDS in the developing world. *Curr Opin Pediatr.* 2009;21(1):83–93.

105. How is an infection with HIV confirmed in the newborn infant?

Because maternal antibody may persist in the infant well into the second year of life, enzyme-linked immunosorbent assay (ELISA) testing and Western blot testing are unreliable until about 18 months of age. Therefore the diagnosis of HIV infection in the newborn usually relies on the direct detection of the virus or viral components in the infant's blood or body fluids by nucleic acid amplification testing (NAAT). The gold standard for diagnostic testing of infants and children <18 months is HIV-1 NAAT, which can directly detect HIV-1 DNA or RNA.

Infants born to HIV-infected women who have not taken antiretroviral therapy should be tested by HIV-1 NAAT during the first 48 hours of life to determine whether in utero acquisition has occurred. If a mother has been taking antiretroviral therapy since the second trimester and has an undetectable viral load during the third trimester and the week before delivery, the risk for in utero transmission is low. An HIV-1 NAAT should be done within the first 14 to 21 days of life and at age 1 to 2 months and again at age 4 to 6 months. HIV can be *presumptively* excluded with two or more negative tests: one at age 14 days or older and the other at age 1 month or older. HIV is considered *definitively* excluded (in nonbreastfed infants) on the basis of two negative virologic tests, with one test performed at age 1 month or older and the other test at age 4 months or older. A negative HIV-1 NAAT at 8 weeks also *presumptively* indicates disease exclusion. Any time a positive result is obtained, testing should be repeated on a second blood sample as soon as possible. The diagnosis of HIV infection is established if two separate samples are found to be positive by PCR testing. For children with negative testing, many experts recommend HIV-1 antibody assay testing at 12 to 18 months to confirm the absence of HIV infection.

AIDS Info. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. www.aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf. Accessed June 14, 2019.

American Academy of Pediatrics. Human immunodeficiency virus infection. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:465–467.

Havens PL, Mofenson LM. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics.* 2009;123(1):175–187.

106. What are the earliest and most common manifestations of congenital HIV infection?

- Most *infants* with congenital HIV infection are asymptomatic at birth, although occasional patients have diffuse lymphadenopathy and hepatosplenomegaly.
- *Older infants* with HIV infection commonly present symptoms of failure to thrive, loss of or failure to obtain normal developmental milestones, mucocutaneous candidiasis (especially after 1 year), hepatosplenomegaly, interstitial pneumonitis, or a combination of these features.
- *Toddlers and older children* with HIV infection may have generalized lymphadenopathy, recurrent bacterial infections, recurrent or chronic parotitis, or progressive encephalopathy and loss of developmental milestones.

Simpkins EP, Siberry GK, Hutton N. Thinking about HIV infection. *Pediatr Rev.* 2009;30(9):337–348.

107. When should *Pneumocystis* prophylaxis begin and end for an HIV-exposed infant?

Historically, the peak incidence of *Pneumocystis* pneumonia in HIV-infected infants occurred at the age of 3 months (range, 4 weeks to 6 months). *Pneumocystis* prophylaxis should be initiated at the age of 4 to 6 weeks and continued until the infant is at least 4 months old unless the infant meets criteria for being *definitively or presumptively* HIV-uninfected. If the HIV status of the child is indeterminate or confirmed positive, *Pneumocystis jiroveci* pneumonia prophylaxis should be continued until the child is 12 months old, at which time reassessment is done (based on CD4 T-lymphocyte counts).

AIDS Info. Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children. www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed June 14, 2019.

108. What is the significance of the "viral load"?

Viral load refers to a quantification of HIV viral RNA as measured by various assays. It is a measure of the degree of infection; the lower limit of detection on ultrasensitive assays is 20 copies/mL, with an upper range of 20 to 50 million copies/mL. Higher levels are associated with increased likelihoods of rapid disease progression and poorer long-term prognosis. Viral loads are used as an ongoing measure of efficacy of treatment, with the goal to achieve an undetectable level for as long as possible. Some investigators prefer the term *HIV plasma RNA*.

109. What are the classes of antiretroviral agents (ARTs) used to treat HIV?

- **Nucleoside and nucleotide analogue reverse transcriptase inhibitors** (NRTIs) competitively inhibit the HIV reverse transcriptase (which converts HIV RNA into DNA) and terminate the elongation of viral DNA. They require intracellular phosphorylation for activation. NRTIs have little or no effect on chronically infected cells because their site of action is before the incorporation of viral DNA into host DNA. This class of drugs includes zidovudine, lamivudine, stavudine, zalcitabine, didanosine (ddI), tenofovir, TAF (tenofovir alafenamide), emtricitabine, and abacavir.

- **Nonnucleoside reverse transcriptase inhibitors** (NNRTIs) also inhibit the HIV reverse transcriptase, although they do so at a different site than do the NRTIs. They bind directly to the active site of HIV reverse transcriptase and do not require activation. This class of drugs includes efavirenz, nevirapine, etravirine, and rilpivirine, among others.
- **Protease inhibitors** (PIs) inhibit the HIV protease, which cuts HIV polyprotein precursors before viral budding. This class of drugs includes atazanavir, darunavir, fosamprenavir, nelfinavir, ritonavir, indinavir, saquinavir, tipranavir, and lopinavir/ritonavir (Kaletra).
- **Integrase inhibitors** block the action of a viral enzyme that inserts the viral genome into the DNA of host cells. This class of drugs includes raltegravir, dolutegravir, and elvitegravir, among others.
- **Entry and fusion inhibitors** include enfuvirtide and maraviroc.

  Generally, triple-drug therapy (so-called potent combination antiretroviral therapy [cART]) is recommended.

Guidelines for treatment of HIV-infected children and adolescents are regularly updated and available at www.aidsinfo.nih.gov/guidelines. Accessed January 24, 2020.

Dobroszycki J, Lee P, Romo DL, et al. Antiretroviral therapy in HIV-infected adolescents: clinical and pharmacologic challenges. *Expert Rev Clin Pharmacol.* 2017;10(5):509–516.

Patel K, Hernán MA, Williams PL, et al. Long-term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: a 10-year follow-up study. *Clin Infect Dis.* 2008;46(11):507–515.

110. What are the common toxicities associated with ART?

- **Anemia** occurs in up to 9% of children receiving AZT (compared with 4% to 5% of those on other regimens) and may be exacerbated in newborns because of the coincident physiologic nadir. **Neutropenia** occurs in 6% to 27% of children receiving ART, particularly those taking AZT.
- **Thrombocytopenia** occurs in 30% of untreated children with HIV infection and is more commonly an initial presentation of HIV infection than a complication of ART. In initial trials, severe thrombocytopenia was seen in 2% of children receiving either ddI and AZT or lamivudine and AZT.
- **Lipodystrophy** can occur in children treated with NRTI, PIs, and efavirenz.
- **GI side effects**: Many children experience adverse GI effects, such as nausea, vomiting, diarrhea, and abdominal pain, especially when AZT and PIs are initiated.
- **CNS effects** are encountered when initiating therapy with efavirenz. Common symptoms include dizziness, drowsiness, vivid dreams, or insomnia. Rarely, seizures have been reported in children.
- **Hepatitis** can occur with almost all ARTs, but is seen less commonly in children than adults. Atazanavir commonly causes indirect hyperbilirubinemia and for this reason is generally not used in neonates.
- **Metabolic abnormalities**, such as dyslipidemia and insulin resistance, can occur with most ART regimens.

AIIDS Info. www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/31/adverse-effects-of-arv. Accessed January 24, 2020.

111. How should nonadherence to HIV medication be addressed?

Noncompliance with highly active antiretroviral therapy (HAART) regimens has been estimated as >50%, with the number being much higher for high-risk groups such as newly diagnosed teenagers and adolescents who acquired HIV perinatally. Close follow-up and simplification of medical therapy, when possible, are key. Recognizing and treating comorbid conditions such as depression and alcohol and drug abuse are also important. Intense follow-up (e.g., weekly) for some high-risk patients is recommended. Youth-friendly technology-based support interventions, such as cell phone and text message follow-up, are showing some promise in improving adherence.

Belzer ME, Naar-King S, Olson J, et al. The use of cell phone support for non-adherent HIV-infected youth and young adults: an initial randomized and controlled intervention trial. *AIDS Behav.* 2014;18:686–696.

112. Should a classroom teacher be told that a child is HIV positive?

There is no absolute requirement to inform a classroom teacher, a school principal, or child care provider about a child's HIV status. It is not necessary for anyone except the child's physician to be aware of the diagnosis. In certain circumstances, such as children with conditions that may lead to blood exposure, such as severe excoriated eczema or bleeding diathesis, it is advisable for a family to discuss this with the child's physician before starting any out-of-home program.

American Academy of Pediatrics. School health. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:144.

113. What are the risk factors for HIV transmission after a needlestick injury?

In a case-controlled study that involved 33 health care workers and 665 controls, the following risk factors were identified:

- High viral inoculum (patient with advanced disease)
- Large volume of blood (from a large-bore hollow needle)
- Deep puncture wound

Overall, the risk for transmission from needles contaminated with the blood of an HIV-infected patient is roughly up to 0.3%. Risk from a puncture wound in a random community setting is thought to be lower. There are no known transmissions from accidental nonoccupational (community) needlesticks.

American Academy of Pediatrics. Human immunodeficiency virus infection. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:475–476.

Nwaiwu CA, Egro FM, Smith S, et al. Seroconversion rate among health care workers exposed to HIV-contaminated body fluids: the University of Pittsburgh 13-year experience. *Am J Infect Control.* 2017;45(8):896–900.

Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. *N Engl J Med.* 1997;337:1485–1490.

KEY POINTS: HUMAN IMMUNODEFICIENCY VIRUS INFECTION

1. Interventions to prevent maternal HIV transmission target the late intrauterine and intrapartum periods, when the highest likelihood of transmission occurs.
2. Most infants with congenital HIV infection are asymptomatic at birth.
3. The gold standard for diagnostic testing of infants and children <18 months is HIV-1 NAAT, which can directly detect HIV-1 DNA or RNA.
4. Viral loads are used as an ongoing measure of treatment efficacy.
5. Triple-therapy (so-called potent cART) is recommended for HIV-infected children.
6. Risk factors for increased HIV transmission after a needlestick injury include a high viral inoculum, large volume of blood, and deep puncture wound.

IMMUNIZATIONS

114. What is the derivation of the word *vaccination*?

Edward Jenner, an eighteenth-century British physician, observed that dairymaids were protected naturally from smallpox, the infectious scourge of the world at that time, after they had developed cowpox, a milder blistering disease. In 1796, he inoculated a young boy with material from fresh cowpox lesions that had been taken from a dairymaid. Two months later, he again inoculated the boy, but with matter from a fresh smallpox lesion. No disease developed, and the science of immunization was born. Because the Latin word for cow was *vacca* and for cowpox was *vaccinia*, Jenner called his new procedure *vaccination*.

Riedel S. Edward Jenner and the history of smallpox and vaccination. *Proc (Bayl Univ Med Cent).* 2005;18(1):21–25.

115. Why are the buttocks a poor location for intramuscular (IM) injections in infants?

The gluteus maximus is not a good choice for injections because of the following:

- The gluteal muscles are incompletely developed in some infants.
- There is a potential for injury to the sciatic nerve or the superior gluteal artery if the injection is misdirected.
- Some vaccinations may be less effective if they are injected into fat (e.g., vaccines for rabies, influenza, and hepatitis B).

If injections into the buttocks are given to older children, the proper site is the gluteus medius in the upper outer quadrant rather than the gluteus maximus, which is more medial.

Zuckerman JN. The importance of injecting vaccines into muscle. *BMJ.* 2000;321(7271):1237–1238.

116. When administering an IM vaccination, is aspiration necessary before injection?

Traditionally, the plunger has been withdrawn to verify that the needle tip is not in a vein. However, when vaccinations are given as recommended in the anterior lateral thigh in an infant or in the deltoid in toddlers >18 months, aspiration before injection is *not* required because no large blood vessels are located at those preferred sites. Additionally, the process of aspiration before injection is more painful and it takes longer to administer the vaccine.

American Academy of Pediatrics. Acute immunization. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:30.

Taddio A, McMurtry CM, Shah V, et al. Reducing pain during vaccine injections: clinical practice guideline. *CMAJ.* 2015;187(13):975–982.

117. Is any risk associated with administering multiple vaccines simultaneously?

Most vaccines can be administered simultaneously at separate sites without concern about effectiveness because the immune response to one vaccine generally does not interfere with immune responses to others. The immune system is capable of recognizing hundreds of thousands of antigens. However, some exceptions exist. For example, the simultaneous administration of cholera vaccine and yellow fever vaccine is associated with interference.

118. Should premature babies receive immunization on the basis of postconception age or chronologic age?

In most cases, premature babies should be immunized in accordance with postnatal chronologic age. If a premature infant is still in the hospital at 2 months of age, the vaccines routinely scheduled for that age should be administered, with the exception of the rotavirus vaccine, which should be deferred until the infant leaves the hospital, because spread of this virus in patient units has been reported. Among premature infants who weigh <2 kg at birth, seroconversion rates to hepatitis B vaccine (HBV) are relatively low when immunization is initiated shortly after birth. Accordingly, in these infants, if the mother is HBsAg negative, immunization should be delayed until just before hospital discharge or until 30 days of age. If HBV is given at birth in infants <2 kg, this should not be counted toward the primary series.

American Academy of Pediatrics. Immunization in special clinical circumstances and hepatitis B. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–68, 419–420.

Gagneur A, Pinquier D, Quach C. Immunization of preterm infants. *Hum Vaccin Immunother.* 2015;11(11):2556–2563.

119. Which vaccines are egg embryo–based vaccines?

Of the immunizations that are commonly administered to children, the **measles–mumps–rubella** (MMR) vaccine and certain **rabies** vaccine preparations are grown in chick embryo fibroblast culture. However, they do not contain significant amounts of egg protein. Children with egg allergy are at low risk for anaphylaxis to MMR and do not require skin testing or special precautions before or during the administration of this vaccine.

120. What is the difference between whole-cell and acellular pertussis vaccines?

Whole-cell pertussis vaccines consist of whole bacteria that have been inactivated and are nonviable. These vaccines contain lipo-oligosaccharide and other cell wall components that result in a high incidence of adverse effects. This vaccine is no longer given in the United States.

Acellular pertussis vaccines contain one or more *B. pertussis* proteins that serve as immunogens. All acellular pertussis vaccines contain at least detoxified pertussis toxin, and most contain other antigens as well, including filamentous hemagglutinin, fimbrial proteins, and pertactin. The acellular vaccines are associated with a much lower incidence of side effects and thus are given for all doses in the United States. Children <7 years of age who have received the whole-cell vaccine abroad should have the series continued with the acellular vaccine formulations.

American Academy of Pediatrics. Pertussis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:624–629.

121. What are the absolute contraindications to pertussis immunization?

The adverse events after pertussis immunization that represent ***absolute contraindications*** to further administration of pertussis vaccine include the following:

- Immediate anaphylactic reaction
- Encephalopathy within 7 days of vaccination

The adverse events that represent ***precautions*** for further administration of pertussis vaccine include the following:

- Moderate or severe acute illness with or without fever
- Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid–containing pertussis vaccine
- History of Arthus-type hypersensitivity reactions (local vasculitis associated with deposition of immune complexes and activation of complement) after a previous dose of tetanus or diphtheria toxoid–containing vaccine
- Unstable or evolving neurologic conditions in children <1 year of age warrant postponement of the vaccine

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American Academy of Pediatrics. Pertussis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:631.

122. How long does protection against pertussis last after immunization?

Vaccine-induced immunity to pertussis is relatively short-lived. On the basis of studies of patients who have been immunized with a whole-cell pertussis vaccine and exposed to a sibling with pertussis, protection against infection is about 80% during the first 3 years after immunization, dropping to 50% at 4 to 7 years and to near 0% at 11 years. Teenagers and adults thus become susceptible to pertussis and serve as vectors for infants, for whom morbidity and mortality are much higher. Because of the slow, steady resurgence of pertussis in the past 2 decades and the availability of an acellular pertussis vaccine combined with diphtheria and tetanus toxoid (Tdap), the Advisory Committee on Immunization Practices of the CDC has recommended that all adolescents >11 years of age should receive a booster dose. Anyone 19 years of age and older who has not received a dose of Tdap should also be vaccinated. This Tdap booster dose can replace one of the 10-year Td booster doses and is especially important for health care workers. Additionally, all pregnant women should receive a Tdap booster during each pregnancy at 27 to 36 weeks.

Centers for Disease Control and Prevention. Pertussis: Summary of Vaccine Recommendations. www.cdc.gov/vaccines/vpd-vac/pertussis/recs-summary.htm. Accessed June 14, 2019.

Saadatian-Elahi M, Plotkin S, Mills KHG, et al. Pertussis: biology, epidemiology and prevention. *Vaccine.* 2016;34(48):5819–5826.

123. What is cocooning?

Pertussis vaccination in the United States has reduced annual pertussis-attributable morbidity and mortality by >90%. Despite this, the annual incidence of pertussis continues to rise. Some of the increase may be attributed to outbreaks in unvaccinated pockets of the country. Infants <6 months of age, who are too young to have completed the primary vaccination series, have up to a 20-fold higher incidence of pertussis than does the general population. Two-thirds of pertussis-infected infants in this age group require hospitalization, and pertussis-related deaths occur almost exclusively in young infants, with the risk being inversely proportional to age and number of infant DTaP vaccine doses received. It is estimated that 75% of infants are infected by a household contact or caregiver. The Advisory Committee on Immunization Practices recommended Tdap vaccination of all adults who come in close contact with children <1 year of age, especially health care workers, to help prevent pertussis-related complications and deaths. This circle of providing protected and protective caregivers is termed *cocooning*.

It is also recommended that all pregnant women receive Tdap during *each* pregnancy at 27 to 36 weeks to facilitate transfer of passively acquired maternal IgG against pertussis to the infant and to ensure immunity.

American Academy of Pediatrics. Pertussis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:632–633.

Forsyth K, Plotkin S, Tan T, et al. Strategies to decrease pertussis transmission to infants. *Pediatrics.* 2015;135(6):e1475–e1482.

124. Which vaccines offer protection against cervical cancer?

Vaccination for **human papillomavirus (HPV).** The first vaccine against HPV (Gardasil) was approved in 2006. It is a quadrivalent vaccine (HPV4) that prevents disease caused by HPV types 6, 11, 16, and 18. A bivalent vaccine (HPV2, Cervarix) was approved in 2009. HPV types 16 and 18 have been causally linked with cervical, vulvar, and vaginal cancers, as well as penile, anal, and oropharyngeal cancers. In December 2014, a nine-valent HPV preparation (Gardasil 9) was approved by the FDA. The latest recommendations are that all boys and girls aged 11 or 12 years should get vaccinated. Catch-up vaccines are recommended for males through age 21 and for females through age 26, men having sex with men (MSM), and immunocompromised people through age 26 (including those with HIV and AIDS).

CDC. Human papilloma virus (HPV). www.cdc.gov/std/hpv/stdfact-hpv.htm#a4. Accessed June 14, 2019.

Harper DM, DeMars LR. HPV vaccines —a review of the first decade. *Gynecol Oncol.* 2017;146(1):196–204.

125. How effective is the pneumococcal conjugate vaccine?

The pneumococcal conjugate vaccine is highly effective against invasive pneumococcal disease, reducing rates by up to 98% for vaccine-associated serotypes in children fully vaccinated during the first 2 years of life. The greatest decline in invasive disease has been in the number of children experiencing bacteremia without a focus. This vaccine has a modest effect on pneumococcal otitis media, preventing about 35% of culture-confirmed cases in young children. Both of these effects were noted after the original heptavalent vaccine (PCV-7) was introduced in 2000. This reduction has continued at a more modest rate following the introduction of a 13-valent (PCV-13) vaccine, which includes serotype 19a, a serotype that has been noted to cause invasive disease but was not included in the PCV-7.

Yildrim I, Shea KM, Pelton SI. Pneumococcal disease in the era of pneumococcal conjugate vaccine. *Infect Dis Clin North Am.* 2015;29(4):679–697.

126. What is the “grandparent effect” of vaccination?

The rate of invasive pneumococcal disease has declined in people >65 years since the introduction of the conjugate pneumococcal vaccine in 2000. Meningitis rates have declined by 54%. Decreased nasopharyngeal carriage among vaccinated infants has likely reduced transmission to older individuals caring for them. This type of “herd effect” in elderly people is referred to as the *grandparent effect*.

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Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *N Engl J Med.* 2009;360(3):244–256.

Millar EV, Watt JP, Bronsdon MA, et al. Indirect effect of 7-valent pneumococcal conjugate vaccine on pneumococcal colonization among unvaccinated household members. *Clin Infect Dis.* 2008;47(8):989–996.

127. What serogroup capable of causing meningococcal infections is lacking in licensed *polyvalent* vaccines in the United States?

Serogroup B isolates account for about one-third of cases of meningococcal disease, but serogroup B polysaccharide is absent from these vaccines. Two quadrivalent meningococcal vaccines (MenACWY) containing capsular polysaccharide from serogroups A, C, Y, and W135 are widely available in the United States, including a plain polysaccharide vaccine that is approved for use in children at least 2 years old and a polysaccharide diphtheria toxoid conjugate vaccine that is licensed for use in individuals 11 to 55 years old. All 11- to 12-year-olds should be routinely vaccinated with the conjugate vaccine, with a booster dose at age 16 years. Vaccination is considered advisable for children at least 2 years old who are in high-risk groups, including those with functional or anatomic asplenia or complement deficiency. A meningococcal vaccine is given to all military recruits in the United States and should be considered for individuals traveling to areas of epidemic or hyperendemic disease. In addition, the current vaccines may be useful as an adjunct to chemoprophylaxis for the control of outbreaks caused by a specific vaccine serogroup.

However, since 2014, two serogroup B meningococcal vaccines (Trumenba and Bexsero) have been approved for use in individuals 10 to 25 years of age. These vaccines do not provide coverage for serogroups A, C, Y, and W135, but are indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. These vaccines have been used in response to outbreaks of serogroup B on college campuses where there have been attributable fatalities.

Centers for Disease Control and Prevention. Meningococcal Disease. www.cdc.gov/meningococcal. Accessed January 20, 2020.

128. How effective is the varicella vaccine if given after exposure to the illness?

The varicella vaccine is highly effective (95% for the prevention of any disease, 100% for the prevention of moderate to severe disease) when used within 36 hours of exposure in an environment involving close contact. Ideally, it is given as soon as possible after the exposure but is recommended up to 5 days after exposure. The reason for the high efficacy is that naturally acquired varicella-zoster virus (VZV) usually takes 5 to 7 days to propagate in the respiratory tract before primary viremia and dissemination occur, whereas vaccine virus may elicit humoral and cellular immunity in significantly less time.

Watson B, Seward J, Yang A, et al. Postexposure effectiveness of varicella vaccine. *Pediatrics.* 2000;105(1 Pt 1):84–88.

129. Is the MMR vaccine effective in preventing measles if given after exposure to the illness?

The measles vaccine, if given within 72 hours of measles exposure, will provide protection in some cases. In the case of a known measles exposure, such as during an outbreak, vaccination within 72 hours is recommended for all unvaccinated contacts, including children as young as 6 months. In children <1 year, this vaccine should not count as part of the primary series, which should continue as usual (with a minimum of 28 days separating vaccines).

130. Of the vaccines included in the routine schedule, which ones contain live viruses?

MMR, **varicella**, **rotavirus**, and **influenza**. Oral polio vaccine is a live attenuated virus vaccine, but it is no longer recommended for routine use. Other live virus vaccines include yellow fever virus vaccines.

KEY POINTS: IMMUNIZATIONS

1. Premature babies should be immunized in accordance with postnatal chronologic age.
2. Without a booster after age 5 years, protection against pertussis infection is about 80% during the first 3 years after immunization, dropping to 50% at 4 to 7 years and to near 0% at 11 years.
3. Live vaccines include MMR, varicella, cold-adapted, live-attenuated influenza, rotavirus, and yellow fever virus.
4. Vaccination of both boys and girls for HPV offers protection against cervical and other forms of cancer.
5. When administering an IM vaccination, aspiration is not necessary before injection.

131. What are the indications for palivizumab?

Palivizumab is a humanized mouse monoclonal antibody that is directed against an RSV protein and that is approved for the prevention of RSV disease in selected children. It is typically administered intramuscularly for five doses, starting in November (or earlier if RSV infections are detected in the community). According to the most recent (2014 and reaffirmed without change in 2017) AAP recommendations, consideration of palivizumab administration includes the following:

- Infants born before 29 weeks in the first year of life
- Infants born before 32 weeks with chronic lung disease, defined as requirement for $>21\%$ oxygen for at least 28 days, also in the first year of life

- Infants and children <2 years with chronic lung disease who are requiring ongoing medical therapy, such as supplemental oxygen, chronic corticosteroid, or diuretic therapy
- Infants <12 months with hemodynamically significant congenital heart disease (i.e., not small ventricular septal defects [VSDs], atrial septal defects [ASDs], or infants with lesions adequately corrected by surgery unless they continue to require medication for congestive heart failure)
- Certain infants with neuromuscular disease or congenital abnormalities of the airways that compromise handling of respiratory secretions in the first year of life
- Infants and children <2 years who will be profoundly immunocompromised during the RSV season

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Committee on Infectious Diseases and Bronchiolitis Guidelines Committee: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics.* 2014;134(2):415–420.

132. What are the recommendations regarding the administration of live-virus vaccines to patients receiving corticosteroid therapy?

Children receiving corticosteroid treatment can become immunosuppressed. Although some uncertainty exists, there is adequate experience to make recommendations about the administration of live-virus vaccines to previously healthy children receiving steroid treatment. In general, live-virus vaccines should not be administered to children who have received prednisone or its equivalent in a dose of 2 mg/kg per day or greater (or ≥20 mg per day for individuals whose weight is >10 kg) for more than 14 days. Treatment for shorter periods; with lower doses; or with topical preparations, local injections, or inhaled corticosteroids should not contraindicate the use of these vaccines. However, immune suppression is possible with these medications and that should be considered at the time of vaccination.

American Academy of Pediatrics. Immunization in special clinical circumstances. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: 84–85.

133. What is thimerosal?

Thimerosal is a mercury-containing preservative that has been used as an additive to vaccines for decades because of its effectiveness in preventing contamination, especially in open, multidose containers. In an effort to reduce exposure to mercury, vaccine manufacturers, the FDA, the AAP, and other groups have worked to remove thimerosal from vaccines that contain this compound. By the end of 2001, all vaccines in the routine schedule for children and adolescents were free or virtually free of thimerosal, with the exception of some inactivated influenza vaccines.

134. Does thimerosal or any vaccine or vaccine combination cause autism?

No. In the totality of studies to date, there is no compelling evidence that thimerosal or any vaccine combination causes autism, attention-deficit/hyperactivity disorder, or other neurodevelopmental disorders.

Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine.* 2014;32(29):3623–3629.

135. How should parents who refuse vaccinations be counseled?

Many parents are aware of alleged controversial issues concerning routine childhood vaccines. A dialogue about specific parental concerns and beliefs should be undertaken calmly and without judgment, because an ongoing discussion may be the most important step to eventual vaccine acceptance. The AAP recommends that generally, physicians should continue to care for children whose families reject immunization. However, if a physician truly believes that they cannot ethically provide care for a family, the professional relationship may be terminated after transfer of care to another physician has been ensured and the parents have been given notice that the physician intends to terminate care. Parents who reject immunization should be advised of local laws restricting entry into school or child care for unvaccinated or undervaccinated children. Documentation of such discussions in the medical record are advised, and sample "Refusal to Vaccinate" forms can be found on the AAP website; many states also have their form for providers generally available on individual state health department websites.

American Academy of Pediatrics. Immunization. www.aap.org/immunization/pediatricians/refusaltovaccinate.html. Accessed June 14, 2019.
American Academy of Pediatrics. Active immunization. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:11–12.
Gilmour J, Harrison C, Asadi L, et al. Childhood immunization: when physicians and parents disagree. *Pediatrics.* 2011;128(Suppl 4):S167–S174.

INFECTIONS WITH RASH

136. What is the traditional numbering of the “original” six exanthemas of childhood, and when were they first described?

- **First disease:** *Measles* (rubeola), 1627
- **Second disease:** *Scarlet fever,* 1627
- **Third disease:** *Rubella,* 1881
- **Fourth disease:** *Filatov-Dukes disease* (described in 1900 and though to be a distinct scarlatiniform type of rubella, attributed more recently to exotoxin-producing *S. aureus*; term is no longer used)
- **Fifth disease:** *Erythema infectiosum*, 1905
- **Sixth disease:** *Roseola infantum* (exanthema subitum), 1910

Weisse ME. The fourth disease: 1900–2000. *Lancet.* 2001;357(9252):299–301.

137. What conditions are associated with fever and petechiae?

The list is extensive because many viral and bacterial pathogens may cause a petechial rash as part of the syndrome or from associated thrombocytopenia or disseminated intravascular coagulopathy. Obviously, not all of these will be high on the differential diagnosis, but should be considered when evaluating the child returning from abroad.

- Human monocytic ehrlichiosis
- Drug hypersensitivity
- Meningococcemia
- Rocky Mountain spotted fever (RMSF)
- Immune thrombocytopenic purpura
- Enteroviral infection
- Henoch-Schönlein purpura
- Staphylococcal sepsis
- Streptococcal infection
- Toxic shock syndrome
- “Infectious mononucleosis”
    - CMV
    - EBV
    - Toxoplasmosis
- Kawasaki disease
- Adenovirus infection
- Dengue fever
- Typhus
- Arenavirus (e.g., Lassa)
- Arboviruses (e.g., yellow fever, Chikungunya)

Razzaq S, Schutze GE. Rocky Mountain spotted fever. *Pediatr Rev.* 2005;26(4):125–129.

138. What are the three Cs of measles?

Cough, coryza, and conjunctivitis. After an incubation period of 4 to 12 days, these symptoms develop and are followed by a characteristic erythematous and maculopapular rash (typically on day 14 after exposure), which spreads from head to feet. The rash is described as morbilliform because it has both macular and papular features (Fig. 10.8).

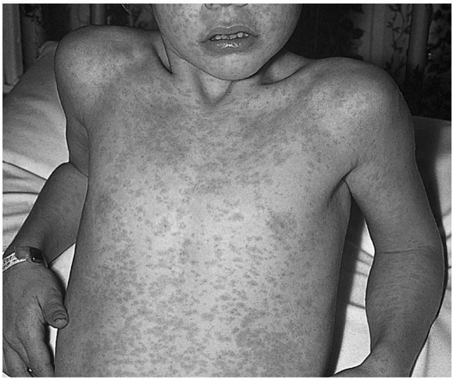

Fig. 10.8 Morbilliform rash of measles. (From Hobson RP. Infectious disease. In Walker BR, Colledge NR, Ralston SH, Penman ID, eds. *Davidson’s Principles and Practice of Medicine.* 22nd ed. Philadelphia, PA: Elsevier; 2014:315.)

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139. What do Koplik spots look like?

Koplik spots are thought to be pathognomonic for measles. They are punctate white-gray papules that occur on a red background, initially opposite the lower molars, but they may spread to involve other parts of the mucosa (Fig. 10.9). However, they may be present for a day or less, are often difficult to appreciate, and should not be relied on to rule in or out the diagnosis.

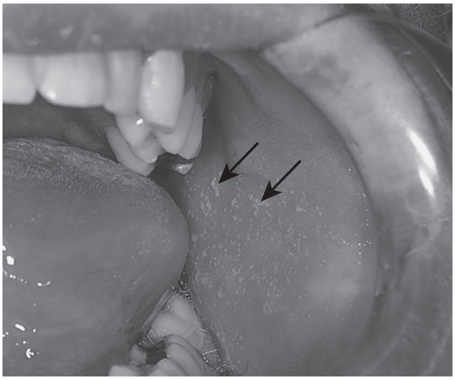

Fig. 10.9 Koplik spots *(arrows).* (From Hobson RP. Infectious disease. In Walker BR, Colledge NR, Ralston SH, Penman ID, eds. *Davidson's Principles and Practice of Medicine.* 22nd ed. Philadelphia, PA: Elsevier; 2014:325.)

140. What is "atypical" about atypical measles?

- Koplik spots are rarely present.
- Conjunctivitis and coryza are not part of the prodrome.
- Rash begins on the distal extremities and spreads toward the head (opposite what is seen in typical measles) or has a nondescript distribution and appearance.
- Respiratory distress with clinical and radiographic signs of pneumonia and pleural effusions are increased in frequency.

Atypical measles occurs primarily in patients who have received inactivated measles vaccine, which was used in the United States from 1963 to 1968 and is therefore more commonly seen in adults.

141. How is measles diagnosed?

Measles IgM antibody requires only a single serum specimen and is diagnostic if positive. A capture IgM test is performed by the CDC. This test should be used to confirm every case of measles that is reported to have some other type of laboratory confirmation. It is important to note that in the first 72 hours after measles rash onset, up to 20% of tests for IgM may be negative. Tests that are negative in the first 72 hours after rash onset should be repeated. PCR-based testing is also available through the CDC. A high index of suspicion is warranted in identifying measles, whether typical or atypical, because many providers, especially those in training, are not likely to have seen cases during their career. This may change as outbreaks in the United States and Canada are becoming more common in the era of vaccine refusal.

CDC. Vaccines and Immunizations. www.cdc.gov/vaccines/pubs/pinkbook/meas.html#diagnosis. Accessed June 14, 2019.

142. Why is postmeasles blindness so common in underdeveloped countries?

Up to 1% of patients with measles in underdeveloped regions experience the progression of measles keratitis to blindness. By contrast, measles keratitis in developed countries is usually self-limited and benign. There are two principal reasons for the progression to blindness among patients with measles in underdeveloped countries:

- **Vitamin A deficiency:** Vitamin A is needed for corneal stromal repair, and a deficiency allows epithelial damage to persist or worsen. Many malnourished children have accompanying vitamin A deficiency, and vitamin A supplements are of benefit during active illness.
- **Malnutrition:** Malnutrition may predispose a patient to corneal superinfection with HSV.

143. How is measles treated?

No antiviral therapy exists for measles. Measles immune globulin has been shown to attenuate the disease if given within 6 days of exposure. It is recommended presently for infants <1 year of age (all infants <6 months or infants <1 year who have missed the window for vaccination), pregnant women without documentation of vaccination or immunity, and certain immunocompromised children. Although the incidence of postmeasles

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blindness is minimal in the United States, the WHO does recommend that vitamin A be given to all children with acute measles, regardless of their country of residence. Vitamin A is administered once daily for 2 days:

- 200,000 IU for children 12 months of age or older
- 100,000 IU for infants 6 through 11 months of age
- 50,000 IU for infants <6 months of age

An additional age-specific dose should be given 2 through 4 weeks later to children with suspicion of vitamin A deficiency.

144. What are the most feared neurologic complications of measles?

- **Acute encephalitis***:* Occurring in about 1 in every 1000 cases, with permanent sequelae in a significant number of cases
- **Subacute sclerosing panencephalitis:** A rare progressive neurodegenerative CNS disease with seizures and intellectual deterioration that occurs on a delayed basis (average time of 11 years) after measles in unvaccinated children, especially those who have had natural measles infection at <1 year of age.

Perry RT, Halsey NA. The clinical significance of measles: a review. *J Infect Dis.* 2004;189(Suppl 1):S4–S16.

145. Which viruses comprise the human herpesviruses (HHV)?

HHV 1 and 2: HSV-1 and HSV-2
HHV 3: VZV
HHV 4: EBV
HHV 5: CMV
HHV 6
HHV 7
HHV 8: *Kaposi sarcoma herpesvirus*

All HHVs share characteristics of virion morphology, basic mode of replication, and capacity for latent and recurrent infections. HSV-1, HSV-2, and VZV are alpha-herpesviruses with short reproductive cycles that establish latent infections, primarily in sensory ganglia. CMV, HHV-6, and HHV-7 are β-herpesviruses with longer reproductive cycles, with latency in white blood cells (WBCs) and other tissues. EBV and HHV-8 are gamma-herpesviruses with specificity for either T or B lymphocytes and latency in lymphoid tissue.

Gilden DH, Mahalingam R, Cohrs RJ, Tyler KL. Herpesvirus infections of the nervous system. *Nat Clin Pract Neurol.* 2006;3(2):82–94.

146. What is the derivation of the word *herpes*?

Herpes comes from the Greek *herpein,* which means "to creep." This describes the tendency of this group of infections both to have spreading cutaneous lesions and to have chronic, latent, or recurrent manifestations.

Beswick TSL. The origin and the use of the word herpes. *Med Hist.* 1962;6:214–232.

147. What are the typical features of roseola (exanthema subitum)?

Roseola occurs most commonly between ages 6 and 24 months. Most children have an abrupt onset of high fever (>102.2°F [39°C]) with no prodrome. Fever usually lasts 3 to 4 days but can range from 1 to 8 days. Within 24 hours of defervescence, a discrete erythematous macular or maculopapular rash appears on the face, neck, and/or trunk. Erythematous papules (Nakayama spots) may be noted on the soft palate and the uvula in two-thirds of patients. Other common findings on examination include mild cervical lymph node enlargement and edematous eyelids. A variety of symptoms can accompany the fever, including diarrhea, cough, coryza, and headache.

148. What causes roseola?

Multiple agents are implicated in the syndrome. HHV-6 was discovered in 1986, and in 1988, Japanese investigators isolated HHV-6 from four children with exanthema subitum. In 1994, HHV-7 was also isolated from children with the clinical features of roseola. *Roseola-like* illnesses are also noted with various echoviruses (including coxsackieviruses A and B), parainfluenza virus, and adenoviruses.

Stone RC, Micali GA, Schwartz RA. Roseola infantum and its causal human herpesviruses. *Int J Dermatol.* 2014;53(4):397–403.

149. How common is HHV-6 infection in children?

Infection with HHV-6 is ubiquitous and occurs with high frequency in infants, 65% of whom have serologic evidence of primary infection by their first birthday. Nearly all children are seropositive by age 4 years. HHV-6 infection results in typical cases of roseola and is also associated with a number of other common pediatric problems, including "fever without localizing findings," nonspecific rash, and EBV-negative mononucleosis. In a study by Hall and colleagues, up to one-third of all febrile seizures in children <2 years were the result of HHV-6 infections. On rare occasions, the virus has been associated with fulminant hepatitis, encephalitis, and a syndrome of massive lymphadenopathy called *Rosai-Dorfman disease*. These manifestations are more common in immune-suppressed children, such as those who have received a bone marrow transplant. Reactivation is common and can also lead to graft-versus-host disease in this population.

Fule Robles JD, Cheuk DK, Ha SY, et al. Human herpesvirus types 6 and 7 infection in pediatric hematopoietic stem cell transplant recipients. *Ann Transplant.* 2014;19:269–276.
Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children. *N Engl J Med.* 1994;331(7):432–438.

150. What is the spectrum of disease caused by parvovirus B19?

- **Erythema infectiosum** (most common; a childhood exanthem, also called *fifth disease* or "slapped-cheek disease" because of the classic appearance of the rash)
- **Papular-purpuric gloves-and-socks syndrome** (self-limited condition of edematous plaques with petechial purpura over the palms and soles)
- **Arthritis** and **arthralgia** (most common in immunocompetent adults)
- Intrauterine infection with **hydrops fetalis**
- **Transient aplastic crisis** in patients with underlying hemolytic disease
- **Persistent infection with chronic anemia** in patients with immunodeficiencies
- **No symptoms**

151. Describe the characteristic rash of RMSF from *Rickettsia rickettsii*

- Usually seen by day 3 of illness (5 to 11 days after tick bite), but may not appear until day 6
- Begins as blanching red macules and maculopapules, which evolve into petechiae in 1 to 3 days
- Begins on flexor surfaces of wrists and ankles and spreads to extremities, face, and trunk within hours
- As rash progresses, may become pigmented with areas of desquamation
- Involves palms and soles

Ten percent to 20% of patients do not develop a rash. Because of the relatively common lack of classic features and the importance of early treatment, RMSF should be considered in the differential diagnosis of any patient in an endemic area who presents with fever, myalgia, severe headache, nausea, and vomiting *without* rash. Presumptive empirical therapy can be begun pending diagnostic studies (biopsy or serology). The risk for death increases when therapy is delayed for more than 5 days.

Blanton LS. The rickettsioses: a practical update. *Infect Dis Clin North Am.* 2019;33(1):213–229.
Dantas-Torres F. Rocky Mountain spotted fever. *Lancet Infect Dis.* 2007;7(11):724–732.

152. Why is doxycycline recommended for *all* ages in patients with suspected RMSF?

Alternatives for older individuals could include tetracycline or a fluoroquinolone, but doxycycline is advised even in younger patients for the following reasons:

- Tetracycline at the recommended dose is associated with dental staining in children <8 years.
- Doxycycline at the recommended dose is unlikely to cause dental staining in younger children.
- Doxycycline is also effective against ehrlichiosis, which can mimic RMSF.
- Fluoroquinolones may cause cartilage damage in juvenile animal models, and their use is not recommended for children for this indication.
- Chloramphenicol, an alternative that has been used in the past, may have serious adverse effects (e.g., aplastic anemia), no oral preparation is available in the United States, and it may be less effective for RMSF than doxycycline.

American Academy of Pediatrics. Rickettsial diseases. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:620–625.
Lochary ME, Lockhart PB, Williams WT Jr. Doxycycline and staining of permanent teeth. *Pediatr Infect Dis J.* 1998;17(5):429–431.

153. How long after exposure to chickenpox (varicella) do symptoms develop?

Ninety-nine percent of patients develop symptoms **between 11 and 20 days after exposure**.

154. What is the risk for varicella-associated complications in normal children 1 to 14 years old?

The most common complications of VZV infection include secondary bacterial skin infections (generally due to streptococci or staphylococci), neurologic syndromes (cerebellitis, encephalitis, transverse myelitis, and Guillain-Barré syndrome), and pneumonia. Thrombocytopenia, arthritis, hepatitis, and glomerulonephritis occur less commonly. Myocarditis, pericarditis, pancreatitis, and orchitis are described but are rare.

The frequency of these complications in normal children is not precisely known, but it is estimated to be low on the basis of hospitalization and mortality data. Before the introduction of the varicella vaccine in 1995, about 4 million cases of chickenpox occurred in the United States each year, resulting in roughly 10,000 hospitalizations and

100 deaths. Since the introduction of routine immunization against varicella, rates of infection have decreased by more than 95%.

Watson B. Varicella: A vaccine preventable disease—a review. *J Infect.* 2002;44(4):220–225.

155. How common are second episodes of varicella after natural infection?

About **1 in 500 cases** involve a second episode. These are more likely to occur in children who develop their first episode during infancy or whose first episode is subclinical or very mild.

Jackson A, Combs JT, Gershon A. Second episodes of varicella: degree and duration of immunity. *Pediatr Infect Dis J.* 1990;9:306.

156. What is herpes zoster?

Reactivated VZV infection. After the primary infection of chickenpox, the virus establishes a latent infection in the dorsal root ganglion. When reactivation occurs, the virus spreads to the skin through nerves, and a typical vesicular pattern along dermatomal lines occurs (Fig. 10.10). In its primary form, the infection is varicella; in its recurrent form, it is zoster, and in common parlance is known as shingles. Varicella is also known as HHV-3 and is one of nine distinct herpesviruses known to cause disease in humans. This has led to the rather confusing name of herpes zoster for the reactivated VZV.

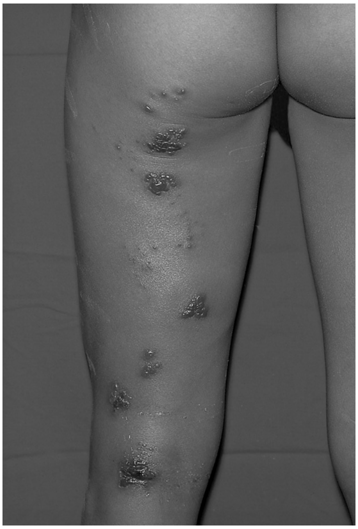

Fig. 10.10 Herpes zoster with distribution along the S1 dermatome. (From Lissauer T, Clayton G. *Illustrated Textbook of Pediatrics.* 2nd ed. London, UK: Mosby; 2001:193.)

157. In children with herpes zoster, what is the distribution of the rash?

Compared with adults, children have relatively more cervical and sacral involvement with resultant extremity and inguinal lesions:

- Fifty percent thoracic
- Twenty percent cervical
- Twenty percent lumbosacral
- Ten percent cranial nerve

If there are lesions on the tip of the nose, herpes zoster keratitis is more likely because of possible involvement of the nasociliary nerve. When the geniculate ganglion is involved, there is risk for developing Ramsay Hunt syndrome, which consists of ear pain with auricular and periauricular vesicles and facial nerve palsy.

Feder HM Jr, Hoss DM. Herpes zoster in otherwise healthy children. *Pediatr Infect Dis J.* 2004;23(5):451–457.

158. Is it possible to get herpes zoster after the varicella vaccine?

Yes. Varicella is a live vaccine, and there was initial concern about how the live, attenuated vaccine strain would act in terms of development of subsequent zoster infection. Zoster is difficult to study because there is a long latent period between acquisition of varicella and development of zoster. However, cohort studies have shown a decreased risk in children of certain age groups, as well as adults, after childhood immunization with the varicella vaccine versus those infected with the wild-type virus. In adults, the use of a live-attenuated varicella-zoster vaccine has been shown to be effective in reducing the incidence and burden of herpes zoster and postherpetic neuralgia.

Weinmann S, Naleway AL, Koppolu P, et al. Incidence of herpes zoster among children: 2003-2014. *Pediatrics.* 2019;144(1):e20182917.
Civen R, Chaves SS, Jumaan A, et al. The incidence and clinical characteristics of herpes zoster among children and adolescents after implementation of varicella vaccination. *Pediatr Infect Dis J.* 2009;28(11):954–959.

159. Should chickenpox be treated with an antiviral medication?

Neither oral acyclovir nor valacyclovir is recommended for routine use in otherwise healthy children with varicella. Early administration after onset of rash results in only a modest decrease in symptoms, as antiviral drugs have a limited window of opportunity for efficacy. In immunocompetent hosts, most virus replication has stopped by 72 hours after onset of rash. By the time the disease is recognized, this window is usually passed. Oral acyclovir or valacyclovir may be considered for people at increased risk for moderate to severe varicella, such as unvaccinated people >12 years of age; children with severe eczema; children receiving long-term salicylate therapy; and people receiving short, intermittent, or inhaled courses of corticosteroids. IV acyclovir instead of oral acyclovir or valacyclovir is recommended for immunocompromised patients, such as children receiving chemotherapy and patients being treated with chronic corticosteroids. Varicella-zoster immune globulin (or intravenous immunoglobulin [IVIG] if this product is not available) can prevent or modify the course of disease if given up to 10 days after exposure and is indicated in certain situations, such as:

- Immunocompromised children without evidence of immunity
- Pregnant women without evidence of immunity
- Newborn infant whose mother had onset of chickenpox within 5 days before delivery or within 48 hours after delivery
- Hospitalized preterm infant (28 weeks or more of gestation) whose mother lacks evidence of immunity against varicella
- Hospitalized preterm infants (<28 weeks of gestation or birth weight 1000 g or less), regardless of maternal immunity

  Treatment with immune globulin is not effective after clinical disease is diagnosed.

CDC. Updated Recommendations for Use of VariZIG—United States, 2013. www.cdc.gov/mmwr/preview/mmwrhtml/mm6228a4.htm. Accessed June 14, 2019.
American Academy of Pediatrics. Varicella-zoster infections. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:969–883.

160. Should healthy children with zoster be treated with antiviral medications?

Routine antiviral therapy is **not indicated**. In general, the prognosis for children with herpes zoster is very good, with extremely low probabilities of postherpetic neuralgia.

161. Who gets herpes gladiatorum?

Herpes gladiatorum is a term used to describe ocular and cutaneous infection with HSV-1, which occurs in **wrestlers** and **rugby players**. The infection is transmitted primarily by direct skin-to-skin contact and is endemic among high school and college wrestlers.

162. What are the features of eczema herpeticum?

Eczema herpeticum (Fig. 10.11) is an extensive cutaneous vesicular eruption that arises from primary infection or reactivation of HSV in those with preexisting skin disease, usually atopic dermatitis (AD). HSV type 1 is the

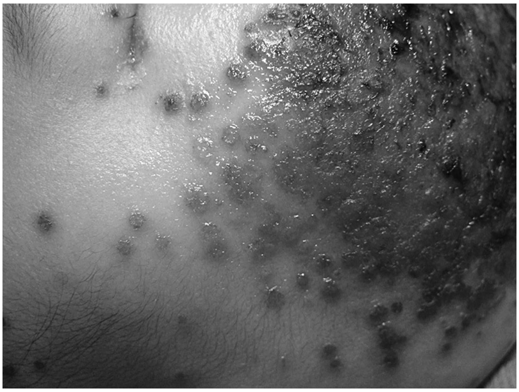

Fig. 10.11 Eczema herpeticum. Note the monomorphic, punched-out ulcers or vesicopustules within eczematous plaques. (From Wolter S, Price HN. Atopic dermatitis. *Pediatr Clin North A* 014;61:247.)

most common pathogen. To further confuse the herpes nomenclature, eczema herpeticum is also known as a form of Kaposi varicelliform eruption, which is a unique skin condition that occurs with viral infections such as HSV or coxsackievirus in those with AD or other underlying dermatologic disease. It is often difficult to distinguish from bacterial superinfection and, in fact, may coexist with a superficial *S. aureus* infection.

163. What causes hand–foot–mouth disease?

Hand–foot–mouth disease is an illness that is caused most commonly by **coxsackie A viruses** (especially A16) or **enterovirus 71**. It is associated with a petechial or vesicular exanthem involving the hands, the feet, and the oral mucosa in the posterior pharynx. Despite its name, it can also affect the buttocks in young children.

164. What is the spectrum of disease caused by enterovirus?

Besides the classic hand–foot–mouth disease, enterovirus may manifest as:

- Upper respiratory tract disease: coryza, herpangina
- Lower respiratory tract illness: pneumonia
- GI illness: vomiting, diarrhea, and hepatitis; rarely pancreatitis, orchitis
- Systemic disease: noted especially in neonates, who may present with an overwhelming sepsis-like syndrome
- Neurologic disease: meningitis, encephalitis, limb paralysis
- Myocarditis

165. Why do real-time PCR positive test results indicate both “rhinovirus/enterovirus”?

Rhinovirus and enterovirus produce clinical syndromes that are distinct, although there generally may be some degree of overlap. However, both viruses are picornaviruses and are classified within the same genus. They share an identical genomic organization and have similar functional RNA secondary structures. As of now, commercially available diagnostics such as the reverse transcriptase polymerase chain reaction (RT-PCR) are unable to distinguish between the two.

INFLUENZA

166. What is the difference between an epidemic, an outbreak, and a pandemic?

- *Epidemic*: Incident cases of an illness (or other health-related events, such as drownings) in a community or region, clearly in excess of normal expectancy
- *Outbreak*: An epidemic limited to a localized increase in the incidence of a disease (e.g., in a town or closed institution), also clearly in excess of normal expectancy
- *Pandemic*: An epidemic that has spread across a large region (e.g., multiple continents)

167. What are the types of influenza viruses?

- **Influenza A** infects many species, including humans, pigs, horses, and birds. It is subtyped on the basis of two surface glycoprotein antigens: *hemagglutinin* (H), of which there are 18 different subtypes; and *neuraminidase* (N), of which there are 11 different subtypes. The subtypes can be further divided into strains; for example, the H1N1 virus developed into a new strain in 2009, replacing the H1N1 strain that had previously caused disease in humans. This new strain was responsible for the 2009 H1N1 pandemic.
- **Influenza B** infects only humans. The disease is generally less severe than influenza A. The virus is not subtyped, but is broken down into lineages and strains.
- **Influenza C** causes very mild disease and has limited public health significance. The influenza vaccine does not protect against influenza C.

168. What are the functions of hemagglutinin and neuraminidase?

Hemagglutinin is a glycoprotein necessary for the initiation of infection because it allows viral binding to sialic acid residues on the respiratory epithelial cells. Progeny virions result after viral replication and bind to the epithelial cells. *Neuraminidase* cleaves sialic acid residues, which permits release of progeny virions into the respiratory tree.

169. What clinical features typically distinguish an infection with an influenza virus from the common cold?

See Table 10.4.

170. What is the difference between “antigenic shift” and “antigenic drift”?

- *Antigenic drift:* A subtle change in the hemagglutinin or neuraminidase gene caused by a point mutation or deletion results in a new strain that requires yearly reformulation of the seasonal influenza vaccine.
- *Antigenic shift:* This occurs much less frequently than antigenic drift (occurring only in influenza A) and involves a profound change in the virus, with a new hemagglutinin or neuraminidase type produced, possibly from another species. For example, simultaneous infection of a host with a human and avian influenza strain can result in genetic reassortment and a novel virus.

171. What made the influenza A H1N1 pandemic strain of 2009 so novel?

The influenza A H1N1 strain caused a worldwide pandemic problem that began in early 2009. This strain was a quadruple reassortment of an influenza A virus involving two swine strains, one human strain, and one avian strain,

Table 10.4 Influenza Versus Cold Symptoms

SIGNS AND SYMPTOMS	INFLUENZA	COLD
Onset	Sudden	Gradual
Fever	>101°F (38.3°C) lasting >3 days	Rare
Cough	Can become severe	Less common
Headache	Prominent	Rare
Myalgia	Severe	Slight
Fatigue	Fatigue lasting >1 wk	Mild
Extreme exhaustion	Early and prominent	Rare
Chest discomfort	Common	Mild
Stuffy nose	Sometimes	Common
Sneezing	Sometimes	Common
Sore throat	Sometimes	Common

From Meissner HC. Reducing the impact of viral respiratory infections in children. *Pediatr Clin North Am.* 2005;52(3):700.

which likely recombined through pigs as an intermediate mammalian host. Components of the 2009 pandemic virus are thought to have derived from the 1918 influenza pandemic. Transmissibility rates were extremely high. Of note, the 1918 influenza pandemic was the most severe in recent history. Worldwide, it was estimated that 500 million people (about one-third of the earth's population at that time) became infected with the influenza virus, with approximately 50 million deaths, including 675,000 in the United States.

Zimmer SM, Burke DS. Historical perspective—emergence of influenza A (H1N1) viruses. *N Engl J Med.* 2009;361(3):279–285.
Morens DM, Taubenberger JK, Fauci AS. The persistent legacy of the 1918 influenza virus. *N Engl J Med.* 2009;361(3):225–229.

172. What main antiviral medications are used as treatment for influenza?

- **Neuraminidase inhibitors:** Oseltamivir (oral), zanamivir (inhaled), and peramivir (IV) prevent release of virions from the host cell. These agents are used against influenza B and A, including pandemic H1N1.
- **Adamantanes (M2 inhibitors):** Amantadine and rimantadine target the M2 protein of influenza A, which is involved in the ion channels of the viral membrane essential for viral replication.

AAP Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2018-2019. *Pediatrics.* 2018;142(4):e20182367.
Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med.* 2005;353(3):1363.

173. Does influenza display resistance to antiviral medications?

Yes. The adamantanes are not effective against influenza B viruses because of the difference in ion channel structure. These drugs are also not effective against the H3N2 and the 2009 H1N1 epidemic strains. The majority of these viruses contain a single amino acid substitution in the M2 protein, which confers adamantane resistance. The H1N1 strain before 2009 (i.e., not the pandemic strain) did have a mutation causing a histidine-to-tyrosine substitution in neuraminidase, making a proportion of these strains resistant to neuraminidase inhibitors. However, this mutation (as are other resistance mechanisms) is sporadic and rare in the pandemic and other recent seasonal strains. Fortunately, the majority of influenza A and B isolates remain susceptible to oseltamivir.

Lee N, Hurt AC. Neuraminidase inhibitor resistance in influenza: a clinical perspective. *Curr Opin Infect Dis.* 2018;31(6):520–526.
Hurt AC. The epidemiology and spread of drug resistant human influenza viruses. *Curr Opin Virol.* 2014;8:22–29.

174. What are the indications for antiviral medications for influenza in children?

- Any child who is hospitalized or has severe or complicated illness
- Children <2 years of age
- Immunosuppressed children
- Children with conditions considered high risk for severe influenza: asthma, cardiac disorders, chronic metabolic disease, renal dysfunction, hemoglobinopathies
- Children who are taking salicylates
- Pregnant women/teens
- Residents of chronic care facilities

- Children with neurologic or neuromuscular disorders

Ideally, antiviral therapy is initiated within 48 hours of symptom onset, but it may still be of some benefit if given at <5 days. An important point of emphasis is that initiation of therapy should not wait for confirmation of diagnosis, especially in high-risk or ill individuals. First-line therapy is oseltamivir.

Centers for Disease Control and Prevention. Antiviral drugs. www.cdc.gov/flu/professionals/antivirals/index.htm. Accessed June 14, 2019.
AAP Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2018-2019. *Pediatrics.* 2018;142(4):e20182367.

175. What complications can be associated with influenza infections?

Death due to exacerbation of an underlying medical condition or invasive coinfection from a secondary bacterial pathogen, including bacterial pneumonia from *S. aureus*, including MRSA, *S. pneumoniae,* or group A streptococci. Other complications include:

- Otitis media
- Myositis (particularly with influenza B)
- Febrile seizures
- Encephalitis, encephalopathy
- Reye syndrome
- Guillain-Barré syndrome
- Transverse myelitis
- Myocarditis, pericarditis

Kondrich J, Rosenthal M. Influenza in children. *Curr Opin Pediatr.* 2017;29(3):297–302.
Mistry RD, Fischer JB, Prasad PA, et al. Severe complications in influenza-like illnesses. *Pediatrics.* 2014;134(3):e684–e690.

176. What bacterial coinfection is most commonly identified in influenza-associated pediatric deaths?

MRSA. In children in the United States, most deaths associated with influenza tend to result either from an exacerbation of an underlying medical condition or invasive coinfection from another pathogen. As the percentage of children colonized with MRSA has increased, this bacterium has assumed a greater role in coinfecting lungs after the influenza virus has damaged the tracheobronchial tree. In a child with a suspected secondary pneumonia during influenza season, coverage for a possible MRSA infection should be considered.

Wong KK, Jain S, Blanton L, et al. Influenza-associated pediatric deaths in the United States, 2004–2012. *Pediatrics.* 2013;132(5):796–804.
Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of *Staphylococcus aureus* coinfection. *Pediatrics.* 2008;122(4):805–811.

LYMPHADENITIS AND LYMPHADENOPATHY

177. What are the most common causes of acute and chronic lymphadenitis in normal, otherwise healthy children?

S. aureus and ***Streptococcus pyogenes*** **(group A streptococci)** account for more than 80% of cases of acute lymphadenitis, while **nontuberculous *Mycobacteria*** and ***Bartonella henselae*** (cat-scratch disease) are the most common causes of chronic lymphadenitis.

178. What infectious etiology should be considered in a toddler with an intensely erythematous but minimally tender submandibular or anterosuperior cervical node?

Nontuberculous mycobacterial infection (NTM) manifests as a group of nodes, which can increase in size, coalesce, and eventually spontaneously rupture to form sinus tracts.

179. How is the diagnosis of NTM disease made?

Definitive diagnosis of NTM infection depends on **culture** and isolation of the organism from infected tissue. Cultures must be sent specifically for *Mycobacteria* to ensure appropriate processing. Histopathologic examination of the tissue cannot adequately differentiate NTM infection from tuberculosis. PCR-based technology is being validated for NTM.

180. How is NTM lymphadenitis treated?

Most experts recommend excision of the infected lymph node. Clarithromycin, rifampin, and ethambutol are effective against many strains of nontuberculous *Mycobacteria* and are generally used when excision is incomplete because of nearby nerve tissue or vascular structures, when surgery is contraindicated, or for recurrent disease. Medical therapy is often prolonged. Organisms can display and develop resistance patterns that may be difficult to manage medically. Some experts have proposed "observation" therapy if this is tolerable to the family and patient, because the majority of isolated lesions will regress without treatment.

Loizos A, Soteriades ES, Pieridou D, Koliou MG. Lymphadenitis by non-tuberculous mycobacteria in children. *Pediatr Int.* 2018;60(12):1062–1067.
Zimmermann P, Tebruegge M, Curtis N, Ritz N. The management of non-tuberculous cervicofacial lymphadenitis in children: a systematic review and meta-analysis. *J Infect.* 2015;71(1):9–18.

181. What infectious etiology should be considered in a child with swollen, tender axillary nodes?

Cat-scratch disease. This entity is caused by *B. henselae*, which is a fastidious, slow-growing, gram-negative bacillus rarely grown in culture. Thus diagnosis is usually made by serologic or PCR tests. This organism is found in the oral flora of kittens, cats, and occasionally dogs.

182. What is the typical course of the lymphadenitis in cat-scratch disease?

An otherwise healthy child or adolescent presents with **symptoms of regional lymphadenopathy** that begin 1 to several weeks after a scratch (unrecalled by many patients). The lymph nodes are usually moderately tender and are associated with overlying erythema and fluctuance. About 10% to 30% eventually suppurate. The lymph nodes most commonly involved are axillary and cervical, but epitrochlear, submandibular, inguinal, and preauricular nodes may be enlarged. Enlarged pectoral nodes are highly suggestive of cat-scratch disease. Fever is usually absent or low grade, but temperatures as high as 104°F (40°C) have been described in 30% to 50% of cases. Infected nodes generally spontaneously resolve without specific therapy. Treatment with 5 days of antibiotics (including azithromycin, ciprofloxacin, trimethoprim-sulfamethoxazole, rifampin, or gentamicin) may speed up recovery, and excision of the infected nodes is not recommended. Treatment with antimicrobial therapy is recommended for severely ill or immunocompromised individuals.

Klotz SA, Ianas V, Elliott SP. Cat-scratch disease. *Am Fam Physician.* 2011;83(2):152–155.
English R. Cat-scratch disease. *Pediatr Rev.* 2006;27(4):123–127.

183. What are other manifestations of cat-scratch disease in addition to lymphadenopathy?

In 20% to 25% of cases, other manifestations may occur, including **Parinaud oculoglandular syndrome** (conjunctivitis, ipsilateral preauricular lymphadenopathy), **prolonged fever of unknown origin**, **encephalitis**, **osteolytic bone lesions**, **neuroretinitis**, **visceral organ involvement** (especially hepatosplenic), and **erythema nodosum**. This organism has also been associated with bacillary angiomatosis (a vascular proliferative disorder with cutaneous and visceral forms) and peliosis hepatitis (a vascular disorder with cystic blood-filled cavities in the liver parenchyma), both of which occur primarily in adults with HIV infection.

184. What are the presentations of EBV infection?

Young children with EBV infection are frequently **asymptomatic**. In adolescents and young adults, infection typically results in **infectious mononucleosis**, which is characterized as follows:

- *Clinical*: Fever, pharyngitis, lymphadenopathy (75% to 95%), splenomegaly (50%)
- *Hematologic*: More than 50% mononuclear cells, more than 10% atypical lymphocytes

A wide variety of symptoms (e.g., malaise, headache, anorexia, myalgias, chills, nausea) can occur. Neurologic presentations are rare but can include encephalitis, meningitis, myelitis, Guillain-Barré syndrome, and cranial or peripheral neuropathies.

EBV is also associated with posttransplant lymphoproliferative disorder, Burkitt lymphoma, nasopharyngeal carcinoma, and undifferentiated T- and B-cell lymphomas.

185. How was the monospot test developed?

In 1932, Paul and Bunnell observed that patients with infectious mononucleosis make antibodies that agglutinate sheep RBCs. These antibodies are referred to as *heterophil antibodies* and serve as the basis for the monospot test, which is a rapid slide agglutination test. Today, horse or beef RBCs are usually used because they are more sensitive to agglutination than are sheep RBCs. Heterophil antibodies can also occur in serum sickness and as a normal variant. If there is clinical confusion, differential absorption can pinpoint the cause. Heterophil antibodies in infectious mononucleosis do not react with guinea pig kidney cells, whereas those of serum sickness do. Normal-variant heterophil antibodies do not react with beef RBCs.

Durbin WA, Sullivan JL. Epstein-Barr virus infections. *Pediatr Rev.* 1994;15(2):63–68.

186. What is the natural course of serologic responses to EBV infection?

Serologic responses to viral components, including viral capsid antigen (VCA), early antigen (EA), and Epstein-Barr nuclear antigen (EBNA), occur in a characteristic time frame (Fig. 10.12) and can assist in distinguishing possible acute from past infections. Acute infection is best characterized by the presence of high titers of VCA IgM or IgG with or without high titers of EA and with no or low titers of EBNA.

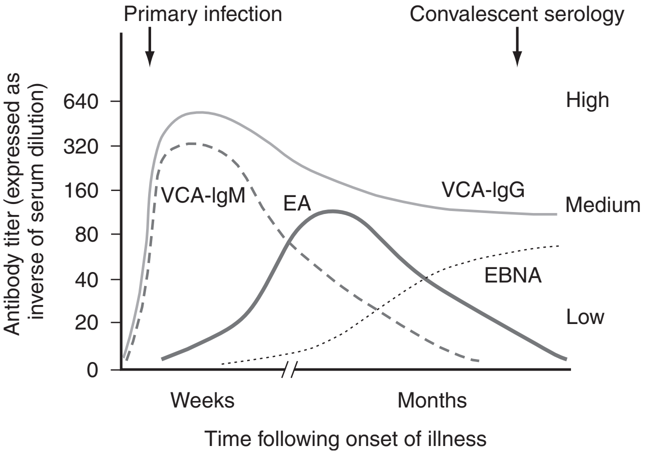

Fig. 10.12 Idealized time course for antibody responses to various EBV antigens after primary infection with the virus. *EA,* Early antigen; *EBNA,* Epstein-Barr nuclear antigen; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *VCA,* viral capsid antigen. (From Katz BZ. Epstein-Barr virus (mononucleosis and lymphoproliferative disorders. In Long SS, ed. *Principles and Practice of Pediatric Infectious Disease.* 4th ed. Philadelphia, PA: Elsevier; 2012:1062.)

187. When are steroids indicated for children with EBV infection?

Among patients with acute EBV infection, steroids should NOT be considered for treatment of uncomplicated mononucleosis. Steroids are indicated for treatment of impending respiratory obstruction as a result of enlarged tonsils, autoimmune hemolytic anemia, aplastic anemia, neurologic disease, and severe life-threatening infection (e.g., liver failure).

188. What are the clinical presentations of acquired CMV infection?

In normal hosts who develop symptomatic acquired CMV infection, clinical manifestations include fever, malaise, and nonspecific aches and pains. The peripheral blood smear reveals an absolute lymphocytosis and many atypical lymphocytes. In contrast with EBV-infectious mononucleosis, exudative pharyngitis is not prominent. Liver involvement is very common, and liver function tests are usually abnormal. Like EBV disease, CMV mononucleosis can persist for several weeks.

189. What is the most common form of tularemia?

Ulceroglandular. Seventy-five percent of cases of tularemia are ulceroglandular. Three to 5 days (range, 1 to 21 days) after exposure, fever, myalgia, headaches, muscle soreness, and regional lymphadenopathy develop. The original lesion is a papule, which ulcerates. Bacteremia may result in multiorgan involvement.

Eliasson H, Broman T, Forsman M, et al. Tularemia: current epidemiology and disease management. *Infect Dis Clin North Am.* 2006;20(2):289–311.

190. What vectors are commonly associated with tularemia?

Francisella tularensis (the causative agent of tularemia) is a zoonotic infection caused by contact with infected animals (rabbits, deer, and muskrats) or invertebrate vectors (ticks). Streptomycin, gentamicin, tetracyclines, chloramphenicol, and fluoroquinolones have been shown to be effective therapy for tularemia.

191. Which other organisms can cause a mononucleosis-like clinical picture?

Toxoplasma gondii, HHV-6, adenovirus, acute HIV infection, group A streptococcal infection, hepatitis B, and rubella

192. Why is it called “mononucleosis”?

This refers to the tendency of certain infections, primarily EBV, to cause the development of morphologically abnormal lymphocytes (which may resemble monocytes), mainly from CD8 + T cells that respond to infection. These atypical cells can account for up to 30% of the WBC count. Atypical lymphocytes may also be present in a host of illnesses, including *B. henselae,* babesiosis, tuberculosis, lymphoma and leukemia, and pertussis.

MENINGITIS

193. What are the most common signs and symptoms of meningitis in infants < 2 months?

The findings of meningitis among neonates and young infants are often *subtle*. **Temperature instability** (fever is more common in full-term infants, whereas hypothermia is more common in preterm infants) occurs in about 60% of

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infected infants. **Neurologic symptoms**, including irritability, poor tone, and lethargy, are noted in 60% of infants with meningitis. Seizures may be the presenting symptom in 20% to 50% of cases. Poor feeding or vomiting can occur as well. On physical examination, about 25% of newborns and young infants have a **bulging fontanel**. Only 13% have nuchal rigidity. Thus the diagnosis of meningitis cannot be excluded in infants on the basis of the absence of these physical findings.

Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. *Clin Perinatol.* 2015;42(1):29–45.
Pong A, Bradley JS. Bacterial meningitis and the newborn infant. *Infect Dis Clin North Am.* 1999;13(3):711–733.

194. What percentage of neonates <30 days of age with bacterial sepsis and positive blood cultures have meningitis?

As many as 20% of such infants will have culture-confirmed meningitis. Conversely, >30% of all infants evaluated for sepsis with negative blood cultures may have meningitis. This is especially notable in low-birth-weight infants.

Garges HP, Moody MA, Cotton CM, et al. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? *Pediatrics.* 2006;117(4):1094–1100.
Stoll BJ, Hansen N, Fanaroff AA, et al. To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. *Pediatrics.* 2004;113(5):1181–1186.

195. What is the most common cause of viral meningitis?

More than 80% of infectious cases are caused by **enteroviruses** (i.e., coxsackievirus, enterovirus, and echovirus).

196. What is the diagnostic test of choice for enteroviral meningitis?

Enteroviruses can be diagnosed by **PCR testing**, which is rapid, sensitive, and specific.

197. What are common arthropod-borne viral causes of meningoencephalitis in the United States?

Several arboviruses can cause meningoencephalitis, including the LaCrosse virus; Powassan virus; West Nile virus, St. Louis, Eastern, and Western equine encephalitis viruses; and the Japanese encephalitis virus. Human infections are most common in the summer and fall when mosquito and tick activity are highest. West Nile virus is an increasingly common cause of aseptic meningitis and meningoencephalitis, especially in the late summer and early fall. Mosquitoes are the primary vector, with a variety of birds (e.g., crows, jays, sparrows) known to serve as hosts. Significant avian mortality is often the first sign of significant West Nile virus activity in a locale. Non–vector-borne transmission (e.g., contaminated blood products, organ transplantation) has been described. Many state health departments and commercial laboratories have PCR-based tests to diagnose these infections.

American Academy of Pediatrics. Arboviruses. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:220–227.
Lanteri MC, Lee TH, Kaidarova Z, et al. West Nile virus nucleic acid persistence in whole blood months after clearance in plasma: implication for transfusion and transplantation safety. *Transfusion.* 2014;54(12):3232–3241.

198. Should computed tomography (CT) scans be performed before an LP during the evaluation of possible meningitis?

Cranial imaging is **not routinely indicated** before LP, unless one of the following is present:

- Signs of herniation (rapid alteration of consciousness, abnormalities of pupillary size and reaction, absence of oculocephalic response, fixed oculomotor deviation of eyes)
- Papilledema
- Abnormalities in posture or respiration
- Generalized seizures (especially tonic), which are often associated with impending cerebral herniation
- Overwhelming shock or sepsis, possibly precluding the procedure
- Concern about a condition mimicking bacterial meningitis (e.g., intracranial mass, lead intoxication, tuberculous meningitis)

Tunkle AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39(9):1267–1284.
Haslam RH. Role of CT in the early management of bacterial meningitis. *J Pediatr.* 1991;119(1 Pt 1):157–159.

199. What is the range of normal parameters for CSF in infants and children who do not have meningitis?

- *Term newborn infants:* WBC count, 0 to 20/mm^3; protein, 30 to 120 mg/dL; glucose, 25 to 120 mg/dL
- *Infants and children:* WBC count, 0 to 9/mm^3; protein, 20 to 40 mg/dL; glucose, 40 to 80 mg/dL

Thomson J, Sucharew H, Cruz AT, et al. Cerebrospinal fluid reference values for young infants undergoing lumbar puncture. *Pediatrics.* 2018;141(3):e20173405.

Kestenbaum LA, Ebberson J, Zorc JJ, et al. Defining cerebrospinal fluid white blood cell count reference values in neonates and young children. *Pediatrics.* 2010;125(2):257–264.

200. If bloody CSF is collected during LP, how is CNS hemorrhage distinguished from a traumatic artifact?

Most often, the blood is a result of the traumatic rupture of small venous plexuses that surround the subarachnoid space, but pathologic bloody fluid can be seen in multiple settings (e.g., subarachnoid hemorrhage, herpes simplex encephalitis). Distinguishing features that suggest pathologic bleeding include the following:

- **Bleeding that does not lessen** during the collection of multiple tubes
- **Xanthochromia** of the CNS supernatant
- **Crenated RBCs** noted microscopically

201. How is a traumatic LP interpreted?

A "*bloody tap*" is a common result of an unsuccessful LP. Numerous formulas have been devised to adjust leukocyte totals in blood-contaminated CSF to determine whether CSF pleocytosis (and thus possible meningitis) is present. However, no formulas in neonates or older children have been reliably useful to guide clinical decisions about bacterial meningitis. Protein measurements are elevated in traumatic LPs. One study of 2600 infants with traumatic LPs determined that for every increased 1000 CSF RBCs/mm^3, CSF protein increased by 1.1 mg/dL.

Lyons TW, Cruz AT, Freedman SB, et al. Correction of cerebrospinal fluid protein in infants with traumatic lumbar punctures. *Pediatr Infect Dis J.* 2017;36(10):1006–1008.
Greenberg RG, Smith PB, Cotten CM, et al. Traumatic lumbar punctures in neonates. *Pediatr Infect Dis J.* 2008;27(12):1047–1051.
Bonsu BK, Harper MB. Corrections for leukocytes and percent of neutrophils do not match observations in blood-contaminated cerebrospinal fluid and have no value over uncorrected cells for diagnosis. *Pediatr Infect Dis J.* 2006;25(1):8–11.

202. What is the best way to position the patient for an LP?

Some studies have shown increase in successful LPs in the **sitting position with flexed hips**, both in children and neonates, compared with the lateral flexed position (although the latter is more commonly practiced in the United States). Data obtained through measurements using ultrasound have shown that the interspinous space may increase in this position, leading to a higher likelihood of entering the appropriate space. Since the diameter of a 1.5-inch, 22-gauge needle is 0.7 mm, even a small difference of 1 to 2 mm in those spaces could contribute to increased success. Data are conflicting whether differences occur in the subarachnoid space between the sitting and lateral flexed positions. Measurement of oxygenation levels via pulse oximetry for preterm infants in the sitting versus lateral knee-flexed positions during an LP have found better oxygenation in the sitting flexed position, which also suggests that this position might be better tolerated and potentially safer for the infant.

Hanson AL, Ros S, Soprano J. Analysis of infant lumbar puncture success rates: sitting flexed versus lateral flexed positions. *Pediatr Emerg Care.* 2014;30(5):311–314.
Oulego-Erroz I, Mora-Matilla M, Alonso-Quintela P, et al. Ultrasound evaluation of lumbar spine anatomy in newborn infants: implications for optimal performance of lumbar puncture. *J Pediatr.* 2014;165(4):862–865.
Gleason CA, Martin RJ, Anderson JV, et al. Optimal position for a spinal tap in preterm infants. *Pediatrics.* 1983;71(1):31–35.

203. How do the CSF findings vary in bacterial, viral, fungal, and tuberculous meningitis in children beyond the neonatal period?

A large overlap in parameters for meningitis caused by different pathogens is possible. For example, bacterial meningitis can be associated with a low WBC count early in the illness, or viral meningitis can be associated with a persistent dominance of neutrophils. The usual findings are summarized in Table 10.5.

Table 10.5 Typical Findings in Bacterial, Viral, Fungal, and Tuberculous Meningitis

CEREBROSPINAL FLUID FINDINGS	BACTERIAL	VIRAL	FUNGAL, TUBERCULOUS
White blood cells per mm^3	>500	<500	<500
Polymorphonuclear neutrophils	$>80\%$	$<50\%$	$<50\%$
Glucose (mg/dL)	<40	>40	<40
Cerebrospinal fluid–to-blood ratio	$<30\%$	$>50\%$	$<30\%$
Protein (mg/dL)	>100	<100	>100

204. What CSF indices help in the diagnosis of bacterial versus viral meningitis?

In the absence of culture data, there is no way one can differentiate bacterial from viral meningitis with certainty. In a study that derived prediction rules for children to determine which group of patients with CSF pleocytosis was most likely to have bacterial rather than viral meningitis, five high-risk criteria were defined. If all were **absent**, 100% of children did not have bacterial meningitis (100% negative-predictive value).

- CSF Gram stain positive
- CSF absolute neutrophil count (ANC) $>$1000 cells/μL
- CSF protein $>$80 mg/dL
- Peripheral blood ANC $>$10,000 cells/μL
- Seizure at or before presentation

Nigrovic LE, Malley R, Kuppermann N. Cerebrospinal fluid pleocytosis in children in the era of bacterial conjugate vaccines. *Pediatr Emerg Care.* 2009;25(2):112–120.

205. When is the best time to obtain a serum glucose level in an infant with suspected meningitis?

Because the stress of an LP can elevate serum glucose, the serum sample is ideally obtained **just before the LP**. When the blood glucose level is elevated acutely, it can take at least 30 minutes before the blood glucose equilibrates with that of the CSF.

206. Does antibiotic therapy before LP affect CSF indices?

Many children with presumptive meningitis are begun on antibiotic therapy before an LP, often because a delay in performing the LP is anticipated. Prior administration of antibiotics does increase the likelihood of falsely negative CSF cultures in patients with bacterial meningitis. Similarly, the CSF Gram stain will still demonstrate bacteria with typical staining properties. Prior antibiotic use decreases the CSF protein concentration and increases the CSF glucose concentration. However, it does not substantially affect the CSF WBC or CSF absolute neutrophil count.

Nigrovic LE, Malley R, Macias CG, et al. Effect of antibiotic pretreatment on cerebrospinal fluid profiles in children with bacterial meningitis. *Pediatrics.* 2008;122(4):726–730.

Nigrovic LE, Kuppermann N, McAdam AJ, Malley R. Cerebrospinal latex agglutination fails to contribute to the microbiologic diagnosis of pretreated children with meningitis. *Pediatr Infect Dis J.* 2004;23(8):786–788.

207. How quickly is the CSF sterilized in children with meningitis?

Data are limited, and trial data are obviously not tenable. In successful therapy, the CSF is usually sterile within 36 to 48 hours of the initiation of antibiotics. In patients with meningococcal meningitis, CSF is typically completely sterile within 2 hours after starting treatment. With other organisms such as pneumococcus, the time until sterilization is generally at least 4 hours. In neonates, the CSF may sterilize more slowly. Furthermore, absence of a positive culture in CSF obtained from the lumbar subarachnoid space does not exclude a positive culture from the ventricles.

Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics.* 2001;108(5):1169–1174.

208. What are the most common organisms responsible for bacterial meningitis in the United States?

0 to $<$1 month old:

- GBS (*Streptococcus agalactiae*)
- *E. coli* (if presents after first week of life, galactosemia should be excluded)
- Miscellaneous Enterobacteriaceae
- *Listeria monocytogenes* (rare)
- *Streptococcus pneumoniae* (rare)
- *S. aureus* (in hospitalized preterm infants)
- Coagulase-negative staphylococci (in hospitalized preterm infants)

1 to $<$3 months old

- GBS
- Gram-negative bacilli
- *S. pneumoniae*
- *N. meningitidis*

3 months to $<$3 years

- *S. pneumoniae*
- *N. meningitidis*
- GBS
- Gram-negative bacilli (including *E. coli* and *H. influenzae*)

3 to 10 years old

- *S. pneumoniae*
- *N. meningitidis*

10 to 18 years old

- *N. meningitidis*

Before the development of conjugate vaccines for important bacterial pathogens, childhood bacterial meningitis was mostly due to *N. meningitidis, S. pneumoniae,* and *H. influenzae* type b (Hib) in infants and children and GBS and *E. coli* in neonates. Although the epidemiology of meningitis in young infants and neonates has remained fairly unchanged, the rate of meningitis due to *S. pneumoniae* has decreased after the introduction of the pneumococcal conjugate vaccines PCV-7 and PCV-13.

Ruiz-Contreras J, Picazo J, Casado-Flores J, et al. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis in children. *Vaccine.* 2017;35(35 Pt B):4646–4651.

Angoulvant F, Levy C, Grimprel E, et al. Early impact of 13-valent pneumococcal conjugate vaccine on community-acquired pneumonia in children. *Clin Infect Dis.* 2014;58:918–924.

209. What are the drugs of choice for the empiric treatment of bacterial meningitis in children >1 month?

Empiric therapy for suspected bacterial meningitis should include both **vancomycin and a third-generation cephalosporin** agent (e.g., cefotaxime, ceftriaxone) because of increasing resistance to penicillin and cephalosporins among some *S. pneumoniae* isolates. These agents also provide excellent coverage against *N. meningitidis* and *H. influenzae.* Treatment failures have been reported when the dosage of vancomycin is <60 mg/kg per day. Vancomycin should not be used alone to treat *S. pneumoniae* meningitis because data from animal models indicate that bactericidal levels may be difficult to maintain in the CSF. The combination of vancomycin plus cefotaxime or ceftriaxone has been shown to produce a synergistic effect in vitro, in animal models, and in the CSF of children with meningitis. Empiric therapy may be expanded for children with suspected bacterial meningitis who have immune deficiency, recent neurosurgery, penetrating head trauma, and anatomic defects.

Kowalsky RH, Jaffe DM. Bacterial meningitis post-PCV7: declining incidence and treatment. *Pediatr Emerg Care.* 2013;29(6):758–766.

Richard GC, Lepe M. Meningitis in children: diagnosis and treatment for the emergency clinician. *Clin Pediatr Emerg Med.* 2013;14:146–156.

210. What is the role of corticosteroids in the treatment of bacterial meningitis?

The inflammatory response plays a critical role in producing the CNS pathology and resultant sequelae of bacterial meningitis. Several studies have demonstrated that treatment with dexamethasone reduces the incidence of hearing loss and other neurologic sequelae in infants and children with meningitis caused by Hib when given before or at the same time as the first dose of antimicrobial therapy. However, a 2013 Cochrane review found no reduction in hearing loss in children with the use of steroids in meningitis due to non-*Haemophilus* species. For cases of meningitis caused by other pathogens, such as *N. meningitides* or *S. pneumoniae,* current AAP recommendations are to "consider" the use of dexamethasone with or shortly before the first dose of antimicrobial therapy after considering the potential risks and benefits. The role of steroids in meningitis caused by other bacterial pathogens remains controversial. In adults, adjuvant corticosteroids decrease mortality in patients with pneumococcal meningitis, but this does not appear to be the case in children. Dexamethasone is not indicated for infants with early-onset sepsis/meningitis.

American Academy of Pediatrics. Pneumococcal infections. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018;643–644.

Wang Y, Liu X, Wang Y, et al. Meta-analysis of adjunctive dexamethasone to improve clinical outcome of bacterial meningitis in children. *Childs Nerv Syst.* 2018;34(2):217–223.

Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev.* 2013;6: CD004405.

211. How long after treatment has been initiated must individuals with meningitis remain on droplet precautions?

Droplet precautions, which mandate a single, closed room and that surgical masks be worn by the staff, are recommended for patients with suspected Hib or meningococcal meningitis, but it can be discontinued after 24 hours of effective antimicrobial therapy.

212. Should children receiving therapy for bacterial meningitis undergo repeat LP?

Repeat LPs are not recommended for uncomplicated courses of meningitis. However, a repeat LP should be strongly considered for the following patients:

- Those with no clinical or poor clinical response to appropriate therapy within 24 to 36 hours
- Those with meningitis caused by penicillin-nonsusceptible or cephalosporin-resistant *S. pneumoniae*
- Those with *S. pneumoniae* who received dexamethasone, because this agent might interfere with the ability to interpret clinical changes (e.g., fever)

- Those with prolonged or recurrent fever
- Those with recurrent meningitis
- Immunocompromised hosts
- Neonates with *Streptococcus agalactiae* and gram-negative meningitis should have a repeat LP after 2 to 3 days of treatment to determine appropriate duration of therapy

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Tunkle AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39(9):1267–1284.

213. What is the accepted duration of treatment for bacterial meningitis?

The duration of antibiotic treatment is based on the causative agent and clinical course. In general, for *uncomplicated* clinical courses, a minimum of 7 days of therapy is required for meningococcal meningitis, 7 to 10 days for *H. influenzae* meningitis, and 10 days for pneumococcal meningitis. Meningitis caused by GBS or *L. monocytogenes* should be treated for 14 to 21 days, and meningitis caused by gram-negative enteric bacilli should be treated for a minimum of 21 days or 21 days after the CSF is sterilized. Among patients with *complications* such as brain abscess, subdural empyema, delayed CSF sterilization, persistence of meningeal signs, or prolonged fever, the duration of therapy may need to be extended and should be individualized.

Repeat CSF cultures should be sterile. The duration of therapy should be extended if organisms are seen on Gram stain or isolated from CSF cultures from the repeat CSF examination. If a repeat LP is done (see question 212), the duration of therapy should be extended if CSF examination at the conclusion of the standard duration of treatment shows >30% neutrophils, CSF glucose of <20 mg/dL, or CSF-to-blood glucose ratio of <20%, respectively.

Tunkle AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39(9):1267–1284.

214. In a patient with meningitis, what are the findings that suggest intracranial complications and provide indications for CT or magnetic resonance imaging (MRI)?

- Prolonged obtundation
- Prolonged irritability
- Seizures developing after day 3 of therapy
- Focal seizures
- Focal neurologic deficits
- Increasing head circumference
- Persistent elevation of CSF protein or neutrophil count
- Recurrence of disease

Oliveira CR, Morriss MC, Mistrot JG, et al. Brain magnetic resonance imaging of infants with bacterial meningitis. *J Pediatr.* 2014;165(1):134–139.

Wubbel L, McCracken GH. Management of bacterial meningitis. *Pediatr Rev.* 1998;19(3):78–84.

215. What are the most common causes of prolonged fever in patients with meningitis?

- Inadequate treatment
- Suppurative disease at other foci (e.g., pericarditis, arthritis, subdural empyema)
- Health care–acquired infection (e.g., CLABSI)
- Thrombophlebitis (related to IV catheters and infusates)
- Drug fever

216. What should the parents of a child with bacterial meningitis be told about long-term outcomes?

Disease resulting from *S. pneumoniae* is associated with considerably more morbidity and mortality than is meningitis caused by *N. meningitidis* or *H. influenzae*. The mortality ranges from 8% to 15%. A 3-year multicenter surveillance study of invasive pneumococcal infections examined outcomes of meningitis caused by *S. pneumoniae* in 180 children. Twenty-five percent of children had evidence of neurologic sequelae at the time of hospital discharge, and 32% had unilateral or bilateral deafness. Predictors of mortality included coma on admission, requirement for mechanical ventilation, and shock. Hearing loss occurs in 5% to 10% of patients with meningitis caused by *H. influenzae* and *N. meningitidis.* Survivors of bacterial meningitis in the neonatal period often have much poorer neurodevelopmental outcomes. Survivors should be followed for hearing loss and other sequelae such as gross motor or cognitive impairment.

Oliveira CR, Morriss MC, Mistrot JG, et al. Brain magnetic resonance imaging of infants with bacterial meningitis. *J Pediatr.* 2014;165(1):134–139.

Koomen I, Grobbee DE, Roord JJ, et al. Hearing loss at school age in survivors of bacterial meningitis: assessment, incidence, and prediction. *Pediatrics.* 2003;112(5):1049–1053.

Arditi M, Mason EO Jr, Bradley JS, et al. Three-year multicenter surveillance of pneumococcal meningitis in children: clinical characteristics and outcome related to penicillin susceptibility and dexamethasone use. *Pediatrics.* 1998;102(5):1087–1097.

217. How should contacts of children with *N. meningitidis* disease be managed?

The attack rate of secondary cases among household contacts of an index patient with invasive disease caused by *N. meningitidis* is 500 to 800 times that of the general population.

Antibiotic prophylaxis is indicated for the following exposed individuals:

- Household members, roommates, intimate contacts, contacts at child care center, young adults exposed in dormitories, and military recruits exposed in training centers within the 7 days before the onset of the index patient's symptoms
- Airplane travelers seated next to an index patient on a flight lasting more than 8 hours or who were exposed to the index patient's respiratory secretions within the 7 days before the onset of the index patient's symptoms
- Medical personnel who were exposed to the index patient's respiratory secretions through intubation, endotracheal tube management, or mouth-to-mouth resuscitation

Options for prophylaxis include:

- Rifampin given twice daily for 2 days
- IM ceftriaxone (1 dose)
- Oral ciprofloxacin (for those $\geq$18 years of age)

Prophylaxis is not recommended for casual contacts at school, work, or hospital setting without direct exposure to the index patient's respiratory secretions.

American Academy of Pediatrics, Meningococcal infections. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:554–556.

218. What is the most common parasitic infection of the CNS?

Neurocysticercosis. This is a tapeworm disease that is most commonly initiated by the ingestion of undercooked pork containing *Taenia solium* larvae. After these larvae mature, eggs from adult tapeworms are then acquired by fecal–oral transmission among humans or by autoinoculation. If hematogenous spread of these eggs to the brain occurs, two types of complications can occur:

- Parenchymal cystic lesions can form a calcified granuloma that can result in seizures and/or headache.
- Extraparenchymal cysticerci can become trapped within the ventricles, foramina, or aqueduct and cause obstructive hydrocephalus manifesting as headache, nausea, vomiting, or change in mental status.

Garcia HH: Neurocysticercosis. *Neurol Clin.* 2018;36(4):851–864.

OCULAR INFECTIONS

219. Among neonates with conjunctivitis, what is the timing for the various etiologies?

- **Chemical**: Onset in <2 days
- ***Neisseria gonorrhoeae***: Onset in 2 to 7 days
- ***C. trachomatis***: Onset in 5 to 14 days
- **HSV**: Onset in 10 to 14 days

220. What is the best method of prophylaxis for ophthalmia neonatorum?

Ophthalmia neonatorum is conjunctivitis in the first month of life. Historically, this referred to *N. gonorrhoeae* as the causative agent from acquisition at birth. Unrecognized and untreated maternal *N. gonorrhoeae* before delivery is now quite rare in the United States. *C. trachomatis* is now the more predominant etiology of neonatal conjunctivitis in the United States. Other bacterial microbes and HSV can be pathogens. As a consequence, erythromycin 0.5% ophthalmic ointment is now used routinely in nurseries in the United States to prevent conjunctivitis, although the efficacy for preventing chlamydial disease (primarily pneumonia) remains unclear. Worldwide, other methods are used, including gentamicin ointment, 2.5% povidone-iodine ophthalmic solution, and silver nitrate drops.

221. Can newborns with chlamydial conjunctivitis be treated with topical therapy alone?

No. Newborns diagnosed with chlamydial conjunctivitis should receive systemic therapy with oral erythromycin for 14 days. One study has suggested that oral azithromycin, 20 mg/kg per day for 3 days, is also effective. Topical therapy will not eradicate the organism from the upper respiratory tract, and it fails to prevent the development of chlamydial pneumonia. Close follow-up evaluation is indicated to ensure the absence of relapse.

Hammerschlag M, Gelling M, Roblin PM, et al. Treatment of neonatal chlamydial conjunctivitis with azithromycin. *Pediatr Infect Dis J.* 1998;17(11):1049–1050.

222. In children with conjunctivitis and otitis media, what are the most likely etiologic agents?

- **Bacterial:** Nontypeable *H. influenzae* is the most common cause of the so-called conjunctivitis-otitis syndrome, which is characterized by concurrent conjunctivitis and otitis media.
- **Viral:** Adenovirus may also cause a conjunctivitis-otitis syndrome.

223. Can bacterial conjunctivitis be distinguished from viral conjunctivitis on clinical grounds alone?

No. Classically, bacterial conjunctivitis is more common in infants and young children, with the discharge being purulent or mucopurulent. A history of sticky eyelids with eyelash closure on awakening is predictive of a bacterial etiology. The most commonly implicated organism is nontypeable *H. influenzae*. Viral conjunctivitis is accompanied by a serous exudate in children of all ages, classically from adenovirus infections. Bacterial infections are commonly associated with otitis media, and otoscopy should be performed on all patients. However, clinical findings can overlap. Both bacteria and viruses can cause unilateral or bilateral symptoms.

Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. *JAMA.* 2013;310(16):1721–1729.
Richards A, Guzman-Cottrill JA. Conjunctivitis. *Pediatr Rev.* 2010;31(5):196–208.
Patel PB, Diaz MC, Bennett JE, et al. Clinical features of bacterial conjunctivitis in children. *Acad Emerg Med.* 2007;14(1):1–5.

224. What is the difference between keratoconjunctivitis and conjunctivitis?

Keratoconjunctivitis is an inflammatory process that involves both the conjunctiva and the cornea. Superficial inflammation of the cornea (keratitis) occurs commonly in association with viral and bacterial conjunctivitis, particularly in adults. Hence, many cases of conjunctivitis are more correctly called *keratoconjunctivitis*. *Epidemic keratoconjunctivitis* is caused by adenovirus serotypes 8, 19, and 37. Some organisms, including measles virus, *P. aeruginosa*, *N. gonorrhoeae*, and HSV, have a propensity to cause more severe infection of the cornea. Infection as a result of these pathogens must be recognized early to prevent corneal scarring with subsequent vision loss.

225. What are the most common causative organisms of acute bacterial conjunctivitis?

- **Neonate:** *S. aureus*, *H. influenzae*, *C. trachomatis*
- **Child:** *S. aureus*, *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*
- **Adolescent/adult:** *S. aureus*, *S. pneumoniae*, Streptococcus spp., *H. influenzae*, *M. catarrhalis*, Acinetobacter spp.

226. How does the treatment vary by age for suspected acute bacterial conjunctivitis?

Topical therapy for *neonatal* chlamydial conjunctivitis should never be used as sole therapy because of the high likelihood of concomitant respiratory tract colonization (which can eventually progress to pneumonia). Infections resulting from *N. gonorrhoeae*, *P. aeruginosa*, Hib, and *N. meningitidis* require systemic therapy to prevent the serious complications seen with these organisms. *Ophthalmic ointments* are usually preferred for infants and young children because they can be instilled more reliably and remain in the eye for a longer time. In older children, *ophthalmic solutions* may be preferred to prevent the blurring of vision that occurs with ointments. In general, the efficacy of ophthalmic ointments is presumed to be superior to that of solutions. However, several antibiotics are available in high-concentration solutions. These "fortified" formulations have not been compared prospectively with other preparations, but they are widely used because of their presumed enhanced efficacy.

227. What should be the specific treatment for a 5-year-old diagnosed with infectious conjunctivitis in an outpatient setting?

This is controversial because viral and bacterial causes (and even allergic conjunctivitis) have clinical overlap, and cultures are not usually obtained on the initial evaluation to obtain a precise diagnosis. Two questions are paramount:

1. *Should empiric antibiotic therapy be started?* Topical antibiotics have been shown to decrease the duration of bacterial conjunctivitis, which does allow an earlier return to school and to work for parents. Treatment can thus reduce the socioeconomic costs of conjunctivitis and help prevent the spread of infection. However, the majority of cases of bacterial conjunctivitis are self-limiting and resolve without treatment. If the cause is indeed viral, antibiotic therapy is unnecessary and may contribute to resistance and unwarranted side effects. Given these options of treatment versus "watchful waiting," physician style and parental preferences hold large sway. Antibiotic treatment should be considered for purulent conjunctivitis, for those with significant discomfort, for contact lens wearers, for immunocompromised patients, and for any cases suspicious for either chlamydial or gonococcal conjunctivitis.
2. *If therapy is begun, which topical antibiotic is preferable?* Options are considerable, including more recent (and expensive) therapies (e.g., fluoroquinolones) designed to counteract the growing resistance patterns of typical pathogens, such as *S. pneumoniae, H. influenzae,* and *Moraxella* spp. Once again, physician style, compliance considerations, and prescription coverage play a large role in choice of antibiotic therapy because clear-cut evidence-based guidelines are lacking.

Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. *JAMA.* 2013;310(16):1721–1729.
Sheikh A, Hurwitz B, van Schayck CP, et al. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database Syst Rev.* 2012;9:CD001211.

228. What is Parinaud oculoglandular syndrome?

Parinaud oculoglandular syndrome is characterized by granulomatous or ulcerating conjunctivitis and prominent preauricular or submandibular adenopathy. The most common cause is cat-scratch disease, but other causes include tularemia, sporotrichosis, tuberculosis, syphilis, and infectious mononucleosis. An important condition in the differential diagnosis to exclude is Kawasaki disease. This condition is distinct from *Parinaud syndrome,* which involves abnormalities of vertical gaze and convergence due to a variety of causes, including pineal gland and midbrain tumors. Of note, both conditions are named for Henri Parinaud, a nineteenth-century physician considered to be the father of French ophthalmology.

229. How is orbital cellulitis distinguished from periorbital (or preseptal) cellulitis?

Periorbital cellulitis involves the tissues anterior to the eyelid septum (Fig. 10.13), whereas *orbital cellulitis* involves the orbit and is sometimes associated with abscess formation and cavernous sinus thrombosis. Distinction between these processes requires assessment of **ocular mobility**, **pupillary reflex**, **visual acuity**, and **globe position** (e.g., proptosis), which are normal in periorbital cellulitis but may be abnormal in orbital cellulitis. An abnormality in any of these four areas mandates radiologic evaluation (usually CT scan of the orbit) and possible surgical drainage.

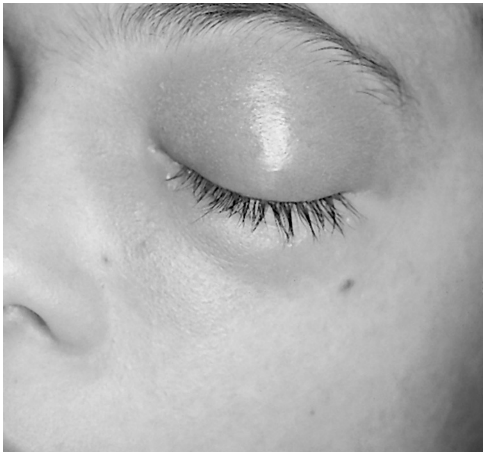

Fig. 10.13 Periorbital cellulitis. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis.* 4th ed. St. Louis, MO: Mosby; 2012:848.)

230. What is the pathogenesis of periorbital and orbital cellulitis?

- *Periorbital*: This cellulitis may result from **direct inoculation** in and around the eyelid, **trauma** (blunt or penetrating), and **spread of microorganisms** from the sinuses or nasopharynx into the preseptal space
- *Orbital*: Most cases originate in nearby paranasal sinuses (especially ethmoid) as a **complication of sinusitis**. The walls (lamina papyracea) of the ethmoid and sphenoid sinuses are paper thin with natural bony dehiscences that allow spread of infection. In addition, orbital and sinus veins anastomose and are valveless, which allows communication of blood flow and easier spread of infection. Complications of orbital cellulitis include subperiosteal orbital abscess, vision loss (from optic neuritis due to surrounding inflammation or thrombophlebitis in adjacent vessels), cavernous sinus thrombophlebitis, and brain abscess.

Sethuraman U, Kamat D. The red eye: evaluation and management. *Clin Pediatr.* 2009;48(6):588–600.

231. What are the most common organisms causing orbital cellulitis?

- **Staphylococci** are the most common organisms causing orbital cellulitis. They are implicated in both orbital and periorbital cellulitis because it is a colonizing organism of both the upper respiratory tract and the skin.
- **Streptococci**:
  - Group A Streptococcus
  - *S. pneumoniae* and other alpha hemolytic strep such as *S. anginosus*

Anaerobic organisms and fungi, such as *Mucor* species and *Aspergillus,* should be considered in immunocompromised hosts.

232. What are treatment options for orbital cellulitis?

Treatment should be guided by the likely epidemiology of the disease. In this era of increasing MRSA colonization in the general population, empiric therapy often comprises coverage for MRSA, such as vancomycin combined with a third-generation cephalosporin, such as ceftriaxone. This choice also has the advantage of good CSF penetration, while an evaluation is being done for intracranial complications. Other choices include vancomycin and ampicillin/sulbactam or piperacillin/tazobactam, with the caveat that these latter agents do not have complete CNS penetration.

233. What is the difference between a hordeolum, a stye, and a chalazion?

- A *hordeolum* is a purulent infection of any one of the sebaceous or apocrine sweat glands of the eyelid, including the glands of Moll and Zeis, which drain near the eyelash follicle, and the meibomian glands, which drain nearer the conjunctiva. Clinically, a hordeolum is recognized as a red, tender swelling. It is usually caused by *S. aureus*.
- A *stye* is an external hordeolum on the skin side of the eyelid.
- A *chalazion* is an internal hordeolum on the conjunctival side of the eyelid.

In all cases, these lesions are treated with warm compresses and topical antibiotic drops or ointment (although their value is debatable) and usually resolve within 7 days. Intralesional triamcinolone injection can be beneficial for a chalazion. A chalazion is more likely to become chronic and require surgical excision.

234. Why is the “ciliary flush” particularly worrisome when evaluating a patient with a pink or red eye?

Ciliary flush (Fig. 10.14) refers to circumcorneal hyperemia in which conjunctival redness is concentrated in the area adjacent to the cornea (limbus). This can be a sign of significant ocular pathology (e.g., keratitis, anterior uveitis, acute angle-closure glaucoma) and requires hastened referral to an ophthalmologist.

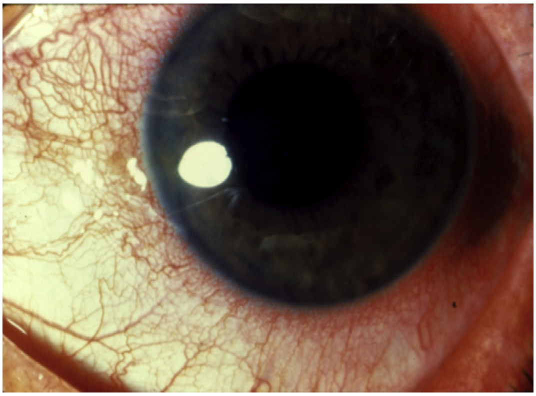

Fig. 10.14 Ciliary flush. Note the circumlimbal hyperemia that becomes less prominent peripherally. (From Dunn JP. *Uveitis. Prim Care*. 2015;42[3]:307.)

235. What organism should not be overlooked when treating ocular infections after penetrating trauma?

Bacillus cereus. This organism is a gram-positive, spore-forming rod, which is ubiquitous in soil. The spores can be very heat resistant. It may be a cause of severe ocular infection after penetrating trauma with contaminated foreign bodies, such as glass, metal, or sticks. Similar to its related bacillus of anthrax fame *(B. anthracis), B. cereus* is generally sensitive to and treated with ciprofloxacin.

OTITIS MEDIA

236. Is ear pulling a reliable sign of infection?

No. In the absence of other signs or symptoms (e.g., fever, URI symptoms), ear pulling alone is a very poor indicator of acute otitis media (AOM).

Baker RB. Is ear pulling associated with ear infection? *Pediatrics.* 1992;90(6):1006–1007.

237. What are the landmarks of the tympanic membrane (TM)?

See Fig. 10.15.

238. What are the most reliable ways, on physical examination, to accurately diagnosis AOM?

Good visualization of the TM and the use of a pneumatic otoscope are key.

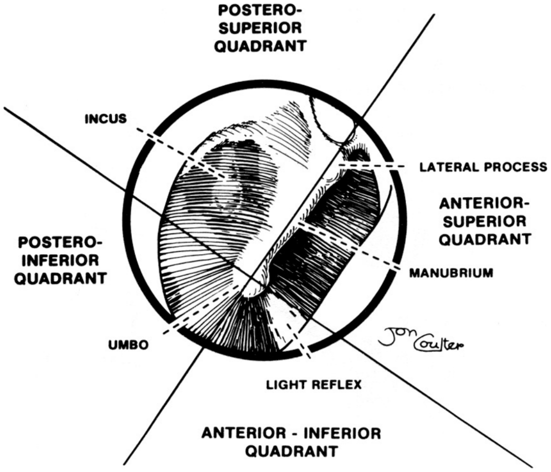
POSTERO-SUPERIOR QUADRANT
INCUS
LATERAL PROCESS
ANTERIOR-SUPERIOR QUADRANT
POSTERO-INFERIOR QUADRANT
MANUBRIUM
UMBO
Jon Coulter
LIGHT REFLEX
ANTERIOR - INFERIOR QUADRANT

Fig. 10.15 Right tympanic membrane. (From Bluestone CD, Klein JO. *Otitis Media in Infants and Children.* Philadelphia, PA: W.B. Saunders; 1988:76.)

- **Visualization of position:** Bulging of the TM implies fluid under pressure, whereas retraction is more commonly seen with effusion rather than suppuration.
- **Color and translucence:** Normal TM color is pearly gray and translucent; cloudiness implies suppuration; distinct redness (especially if unilateral) can indicate infection, but can be seen in other settings, particularly with high fever. Marked redness without TM bulging is unusual in AOM.
- **Mobility:** Impaired mobility of the TM to positive pressure by pneumatic otoscopy implies a fluid-filled space.

Shaikh N, Hoberman A, Kaleida PH, et al. Otoscopic signs of otitis media. *Pediatr Infect Dis J.* 2011;30(10):822–826.
Rothman R, Owens T, Simel DL. Does this child have acute otitis media? *JAMA.* 2003;290(12):1633–1640.

239. What are the most common viral and bacterial agents that cause AOM?

Tympanocentesis is now rarely done except under the auspices of tympanostomy tube placement, but historically it has yielded bacteria and/or viruses in up to 96% of patients with AOM (66% bacteria and viruses together, 27% bacteria alone, and 4% virus alone).

The most common organisms that are recovered from patients with AOM (either from the nasopharynx or middle ear) are *S. pneumoniae,* nontypeable *H. influenzae,* and *M. catarrhalis.* The microbiology of AOM has changed with the introduction of the initial seven-valent pneumococcal conjugate vaccine (PCV-7) and later the 13-valent pneumococcal conjugate vaccine (PCV-13), with a shift toward increasing prevalence of *H. influenzae,* and serotypes of *S. pneumonia* that display antibiotic resistance or are not covered by PCV-7 or PCV-13.

Levy C, Varon E, Ouldali N, et al. Bacterial causes of otitis media with spontaneous perforation of the tympanic membrane in the era of 13 valent pneumococcal conjugate vaccine. *PLoS One.* 2019;14(2):e0211712.
Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era. *Pediatrics.* 2017;140(3):e20170181.

240. What is the “watchful waiting” approach for otitis media?

This is the observational option (“watchful waiting”) for patients >2 years for whom the diagnosis of otitis media is certain but the illness is not severe. Anticipating a high percentage of spontaneous improvement, clinicians defer antibiotic therapy. If the patient does not improve with observation for 48 to 72 hours, antibiotics are initiated. The intent is to reduce potentially unnecessary antibiotics. When using this option, reliable follow-up *must* be ensured.

241. Should all children with AOM be treated with antibiotics?

Observation as initial management for AOM in properly selected children does not increase the risk for serious complications, provided that follow-up is ensured and a rescue antibiotic is given for persistent or worsening symptoms. AAP guidelines published in 2013 endorse the following practices:

Antibiotic therapy should be prescribed for AOM (bilateral or unilateral) in children ≥6 months with severe signs or symptoms:

- Severe AOM is defined as moderate or severe otalgia or otalgia for at least 48 hours or temperature ≥102.2°F (39°C)

Children 6 months to 23 months of age without severe signs or symptoms:

- Antibiotic therapy should be prescribed for bilateral AOM in young children.
- For nonsevere unilateral AOM in young children: it is reasonable to offer observation with close follow-up based on joint decision-making with caregivers, provided that follow-up can be ensured and there is a mechanism to begin antibiotic therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms.

In children $>$23 months of age with AOM (unilateral or bilateral) without severe signs or symptoms, it is reasonable to offer observation with close follow-up.

Brinker DL Jr, MacGeorge EL, Hackman N. Diagnostic accuracy, prescription behavior, and watchful waiting efficacy for pediatric acute otitis media. *Clin Pediatr.* 2019;58(1):60–65.

Lieberthal A, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics.* 2013;131(3):e964–e999.

Spiro DM, Tay KY, Arnold DH, et al. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. *JAMA.* 2006;296(10):1235–1241.

242. What is the recommended therapy for children for whom treatment for AOM is indicated?

High-dose (80 to 90 mg/kg per day in two divided doses) amoxicillin is the standard recommendation for children who have not taken amoxicillin in the previous 30 days and who do not have concurrent conjunctivitis (indicating *H. influenza* infection and the need for a β-lactamase inhibitor). High-dose therapy has been recommended due to concerns of penicillin-resistant *S. pneumoniae.* Because surveillance studies are demonstrating decreasing percentages of otitis media caused by *S. pneumoniae* as a result of conjugate pneumococcal vaccinations and increasing percentages caused by beta-lactamase–producing *H. influenzae and M. catarrhalis* (both resistant to amoxicillin), some experts have suggested first-line use of amoxicillin-clavulanate at regular doses.

Wald ER, DeMuri GP. Antibiotic recommendations for acute otitis media and acute bacterial sinusitis: conundrum no more. *Pediatr Infect Dis J.* 2018;37(12):1255–1257.

Harrison CJ. Amoxicillin is the most cost-effective therapy for acute otitis media: the culmination of 40 years of research. *J Pediatr.* 2017;189:5–8.e1.

Lieberthal A, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics.* 2013;131(3):e964–e999.

243. After an acute episode of otitis media, how long does the middle ear effusion persist?

About 70% of patients will continue to have an effusion at 2 weeks, 40% at 1 month, 20% at 2 months, and 5% to 10% at 3 months.

Teele DW, Klein JO, Rosner BA. Epidemiology of otitis media in children. *Ann Otol Rhinol Laryngol Suppl.* 1980;89(3 Pt 2):5–6.

244. What are the indications for tympanostomy tubes?

Tympanostomy tubes are most commonly inserted for the treatment of otitis media with effusion (OME) or for prophylaxis against recurrent otitis media. American Academy of Otolaryngology – Head and Neck Surgery recommendations state that tympanostomy tubes may be offered for recurrent AOM (three episodes in 6 months or four episodes in 1 year, with one episode in the preceding 6 months). This recommendation is based on limited trial data. For patients with recurrent otitis media, the benefit of tube placement is modest and must be weighed against the risk for complications, which include sclerosis, retraction, atrophy of the eardrum, and complication related to general anesthesia.

Vanneste P, Page C. Otitis media with effusion in children: pathophysiology, diagnosis and treatment. *J Otol.* 2019;14(2):33–39.

Steele DW, Adam GP, Di M, et al. Effectiveness of tympanostomy tubes for otitis media: a meta-analysis. *Pediatrics.* 2017;139(6):e20170125.

Rosenfield RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. *Otolaryngol Head Neck Surg.* 2013;149(1 Suppl 1):S1–S35.

245. Should a child with tympanostomy tubes be allowed to swim?

Otolaryngologists differ widely in their guidance to parents about issues of swimming and bathing. Controlled studies have shown that the rate of otorrhea is similar between nonswimmers (15%) and surface swimmers without earplugs (20%). Neither earplugs nor prophylactic eardrops appear to be necessary for most children who swim at the surface in the ocean or in a pool. If diving or underwater swimming is planned, fitted earplugs are often recommended. Bath water with shampooing can cause inflammatory changes in the middle ear, and thus earplugs should be used if head dunking is anticipated during bathing. An in vitro study (using a head model) found water entry greatest with submersion in soapy water and with deeper swimming.

Wilcox LJ, Darrow DH. Should water precautions be recommended for children with tympanostomy tubes? *Laryngoscope.* 2014;124(1):10–11.

Hebert RL II, King GE, Bent JP III. Tympanostomy tubes and water exposure: a practical model. *Arch Otolaryngol Head Neck Surg.* 1998;124(10):1118–1121.

246. A child with the acute onset of ear pain and double vision likely has what condition?

Gradenigo syndrome is an *acquired paralysis* of the abducens muscle with *pain* in the area that is served by the ipsilateral trigeminal nerve. It is caused by inflammation of the sixth cranial nerve in the petrous portion, with involvement of the gasserian ganglion. The inflammation is usually the result of infection from otitis media or mastoiditis. Symptoms may include weakness of lateral gaze on the affected side, double vision, pain, photophobia, tearing, and hyperesthesia.

247. What are differences between acute and chronic mastoiditis?

- *Acute mastoiditis*: Presents as complication of AOM with retroauricular inflammation (swelling and tenderness) and protrusion of the auricle; patients are younger; most likely causes are *S. pneumoniae* and *S. pyogenes,* with MRSA increasing as a pathogen.
- *Chronic mastoiditis*: Typically with more extensive history of otitis media, including tympanostomy tubes; <50% with retroauricular swelling and tenderness; patients are older; most likely cause is *P. aeruginosa,* with MRSA also increasing as a pathogen.

Lin HW, Shargorodsky J, Gopen Q. Clinical strategies for the management of acute mastoiditis in the pediatric population. *Clin Pediatr.* 2010;49(2):110–115.
Stähelin-Massik J, Podvinec M, Jakscha J, et al. Mastoiditis in children: a prospective, observational study comparing clinical presentation, microbiology, computed tomography, surgical findings and histology. *Eur J Pediatr.* 2008;167(5):541–548.

248. What are the potential complications of mastoiditis?

Epidural abscess, **brain abscess**, **cervical abscess**, **sinus vein thrombosis**, **cervical vein thrombosis**, and **sensorineural hearing loss** are potential complications.

249. What famous playwright died of mastoiditis?

Oscar Wilde died from CNS dissemination of mastoiditis, likely due to *S. pneumoniae*. This was especially ironic, as his estranged father and Irish eye and ear surgeon, Sir William Wilde, introduced the retroauricular incision, which at the time was a novel surgical approach for the treatment of mastoiditis.

Bento RF, Fonseca ACO. A brief history of mastoidectomy. *Int Arch Otorhinolaryngol.* 2013;17(2):168–178.

PHARYNGEAL AND LARYNGEAL INFECTIONS

250. Can group A β-hemolytic streptococcal (GAS) pharyngitis reliably be distinguished from viral causes?

Streptococcal pharyngitis is a disease with variable clinical manifestations. Clues that suggest streptococcal disease include the abrupt onset of headache, fever, and sore throat with the subsequent development of tender cervical lymphadenopathy, tonsillar exudate, and palatal petechiae in the winter or early spring. The presence of concurrent conjunctivitis, rhinitis, cough, or diarrhea suggests a viral process. The physical findings are by no means diagnostic and, when present, are more commonly found in children >3 years. Even the most skilled clinician cannot exceed an accuracy rate of about 75%. A throat culture or a rapid antigen test is essential for confirming streptococcal infection.

Thai TN, Dale AP, Ebell MH. Signs and symptoms of group A versus non-group A strep throat: a meta-analysis. *Fam Pract.* 2018;35(3):231–238.
Wessels MR. Streptococcal pharyngitis. *N Engl J Med.* 2011;364(7):648–655.

251. What is the typical rash of scarlet fever?

The rash, which is caused by a streptococcal pyrogenic exotoxin, usually begins on the neck, face, and upper trunk and generalizes to the remainder of the body over 1 to 2 days. Palms and soles are usually spared. The rash has a sandpaper-like texture—pinpoint, erythematous, blanchable papules. The erythema (and some petechiae from fragile capillaries) may be prominent as lines of deeper red in skin folds (Pastia lines). Over 5 to 7 days, the rash fades and later is followed by desquamation, particularly on the hands, feet, axillae, and groin.

252. Why is a throat culture for GAS advised if a rapid antigen detection test is negative?

A variety of antigen detection tests are available. They have a high degree of specificity but a lower sensitivity. Thus a negative test does not exclude the possibility of GAS and a throat culture is recommended. In adults, however, because of the low incidence of GAS infections and the extremely low risk for acute rheumatic fever, the Infectious Diseases Society of America (IDSA) recommends that the diagnosis can be made on the basis of antigen detection testing alone without confirmation of a negative antigen test by a negative throat culture. Newer NAATs may obviate the need for culture-based backup testing and are being utilized in some emergency departments.

Luo R, Sickler J, Vahidnia F, et al. Diagnosis and management of group A streptococcal pharyngitis in the United States, 2011–2015. *BMC Infect Dis.* 2019;19(1):193.

Cohen DM, Russo ME, Jaggi P, et al. Multicenter clinical evaluation of the novel Alere I strep A isothermal nucleic acid amplification test. *J Clin Microbiol.* 2015;53(7):2258–2261.

Shulman S, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2012;55(10):e86–e102.

253. What is the rationale for the treatment of GAS pharyngitis?

- To prevent acute rheumatic fever (even though there is a low incidence of acute rheumatic fever in the United States, worldwide rheumatic heart disease is the leading cause of cardiovascular death during the first 5 decades of life)
- To shorten the course of the illness, including headache, sore throat, and lymph node tenderness
- To reduce the spread of infection
- To prevent suppurative complications

254. What is the recommended treatment for GAS pharyngitis?

Except in a patient with a history of penicillin allergy, the recommended therapy is IM benzathine G or oral penicillin V or amoxicillin for a duration of 10 days. Amoxicillin suspension is often prescribed rather than penicillin suspension because of better taste. First-line therapy for penicillin-allergic patients is narrow-spectrum cephalosporins (e.g., cephalexin, cefadroxil), clindamycin, or a macrolide (e.g., azithromycin, clarithromycin). Tetracyclines, trimethoprim-sulfamethoxazole, and older fluoroquinolones (e.g., ciprofloxacin) are not recommended.

Shulman S, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2012;55(10):e86–e102.

255. Why do some clinicians use treatments other than penicillins for GAS pharyngitis?

Although 100% of GAS cases have demonstrated in vitro susceptibility to penicillins, normal oropharyngeal flora (including *S. aureus* and *M. catarrhalis*) may produce β-lactamases that can inactivate penicillin and amoxicillin in the local oral environment. Other factors, including tolerability, cost, and prior responses to treatment, are also involved in the choice of antibiotics.

Brook I, Gober AE. Failure to eradicate streptococci and beta-lactamase producing bacteria. *Acta Paediatr.* 2008;97(2):193–195.

256. How does one differentiate a patient with a sore throat who is a streptococcal carrier with an intercurrent viral pharyngitis from one who is having repeated episodes of GAS pharyngitis?

Streptococcal carrier

- Signs and symptoms of viral infection (rhinorrhea, cough, conjunctivitis, diarrhea)
- Little clinical response to antibiotics (sometimes difficult to assess because of the self-resolving nature of viral infections)
- Group A *Streptococcus* present on cultures between episodes
- No serologic response to infection (i.e., anti-streptolysin O, anti-DNase B)
- Same serotype of group A *Streptococcus* in sequential cultures

Recurrent group A streptococcal pharyngitis

- Signs and symptoms consistent with group A streptococcal infection
- Marked clinical response to antibiotics
- No group A *Streptococcus* on cultures between episodes
- Positive serologic response to infection
- Different serotypes of group A *Streptococcus* on sequential cultures

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DeMuri GP, Wald ER. The group A streptococcal carrier state reviewed: still an enigma. *J Pediatr Infect Dis Soc.* 2014;3(4):336–342.

Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. *Pediatrics.* 2012;126(3):e557–e564.

257. When can children treated for positive streptococcal throat cultures return to school or day care?

AAP guidelines advise that children can return once they are well appearing and at least 12 hours have passed since initiation of appropriate antibiotic therapy.

American Academy of Pediatrics. Group A streptococcal infections. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:761.

258. How commonly do children <3 years of age develop GAS pharyngitis?

Traditional teaching has been that toddlers rarely develop streptococcal pharyngitis. However, studies have indicated that the incidence of infection and the prevalence of carriage are greater than previously thought. In studies of patients <2 years with fever and clinical pharyngitis, 4% to 6% were positive for GAS; among well children, the carrier rate is about 6%. In young children, GAS infection is more commonly associated with a syndrome of fever, mucopurulent rhinitis, and diffuse adenopathy. The rate of rheumatic fever is exceedingly low in children <3 years.

Shulman S, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2012;55(10):e86–e102.

Berkovitch M, Vaida A, Zhovtis D, et al. Group A streptococcal pharyngotonsillitis in children less than 2 years of age—more common than is thought. *Clin Pediatr.* 1999;38(6):365–366.

Nussinovitch M, Finkelstein Y, Amir J, Varsano I. Group A beta-hemolytic streptococcal pharyngitis in preschool children aged 3 months to 5 years. *Clin Pediatr.* 1999;38(6):357–360.

259. How long after the development of streptococcal pharyngitis can treatment be initiated and still effectively prevent rheumatic fever?

Treatment should be started as soon as possible, but little is lost in waiting for throat culture results to establish the diagnosis. Antibiotic treatment prevents acute rheumatic fever even when therapy is initiated as long as **9 days** after the onset of the acute illness.

Catanzaro FJ, Stetson CA, Morris AJ, et al. The role of the streptococcus in the pathogenesis of rheumatic fever. *Am J Med.* 1954;17(6):749–756.

KEY POINTS: PHARYNGITIS

1. Clinical pictures of viral and streptococcal pharyngitis have significant clinical overlap.
2. Tetracyclines, trimethoprim-sulfamethoxazole, and older fluoroquinolones (e.g., ciprofloxacin) are not recommended for the treatment of GAS pharyngitis.
3. Antibiotic treatment prevents acute rheumatic fever even when therapy is initiated as long as 9 days after the onset of acute illness.
4. Although the incidence of rheumatic fever is low in the United States, worldwide, it is the leading cause of cardiovascular death during the first five decades of life.

260. What diagnosis should be suspected in a teenager with pharyngitis followed by multifocal pneumonia and sepsis?

Lemierre syndrome. This is a *septic thrombophlebitis* of the internal jugular vein that is typically caused by anaerobic organisms, such as the gram-negative rodlike *Fusobacterium necrophorum*. The illness begins as a pharyngitis or tonsillitis; once thrombophlebitis develops, it results in seeding of multiple organs with septic emboli. Pneumonia may lead to respiratory failure in untreated cases. Ultrasonography of the jugular vessels and CT scan of the chest are helpful for establishing the diagnosis. Anaerobic organisms may be difficult to capture with traditional cultures.

261. What is the difference between herpangina and Ludwig angina?

- *Herpangina* is a common viral infection during the summer and fall and is characterized by posterior pharyngeal, buccal, and palatal vesicles and ulcers. Coxsackieviruses A and B and echoviruses are the most common causative agents. In young children, it is often accompanied by a high temperature (103° to 104°F [39.4° to 40°C]). Herpangina is distinguished from HSV infections of the mouth, which are more anterior and involve the lips, tongue, and gingiva.
- *Ludwig angina* is an acute diffuse infection (usually bacterial due to mixed anaerobes) of the submandibular and sublingual spaces with brawny induration of the floor of the mouth and tongue. Airway obstruction can occur. The infections usually follow oral cavity injuries or dental complications (e.g., extractions, impactions).

Lin HW, O'Neill A, Cunningham MJ. Ludwig's angina in the pediatric population. *Clin Pediatr.* 2009;48(6):583–587.

262. What is quinsy?

Quinsy is a **peritonsillar abscess**. George Washington's death has traditionally been attributed to quinsy, but historians have debated whether an alternative pathologic explanation—epiglottitis—was more likely.

Morens DM. Death of a president. *N Engl J Med.* 1999;341(24):1845–1850.

263. How is a peritonsillar abscess distinguished from peritonsillar cellulitis?

A *peritonsillar abscess* is diagnosed when a discrete mass is noted, usually in school-age children and adolescents. The bulging abscess causes lateral displacement of the uvula. Trismus, due to spasm of masticator muscles, occurs more commonly in the setting of abscess than does simple cellulitis, which is characterized by signs of diffuse inflammation without a mass. Many patients have a "hot potato" voice, a muffled voice caused by palatal edema and spasm of the internal pterygoid muscle that elevates the palate.

Galioto NJ. Peritonsillar abscess. *Am Fam Physician.* 2017;95(8):501–506.

264. What radiographic features suggest the diagnosis of a retropharyngeal abscess?

When a patient's neck is extended, a measurement of the prevertebral space that exceeds two times the diameter of the C2 vertebra suggests an abscess (Fig. 10.16). Pockets of air in the prevertebral space also suggest abscess. The retropharynx extends to T1 in the superior mediastinum, so empyema or mediastinitis is also possible whenever a retropharyngeal abscess is identified. CT scanning can delineate the extent of these deep neck infections.

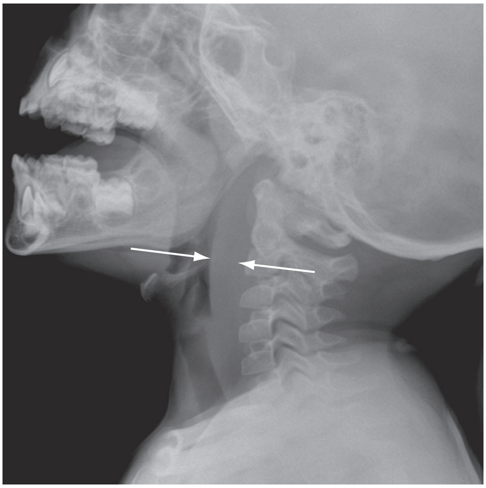

Fig. 10.16 Thickening of the prevertebral soft tissues *(white arrows)* in a 3-year-old boy with neck stiffness due to a retropharyngeal abscess. (From Taussig LM, Landau LI, eds. *Pediatric Respiratory Medicine.* 2nd ed. Philadelphia, PA: Mosby; 2008:147.)

265. Which age group is most susceptible to retropharyngeal abscess?

This disease is most common in children **between the ages of 1 and 6 years**. There are several small lymph nodes in the retropharynx that usually disappear by the age of 4 or 5. These lymph nodes drain the posterior nasal passages and nasopharynx, and they may become involved if those sites are infected.

266. What are the indications for tonsillectomy in children 1 to 18 years old?

- Obstructive sleep apnea syndrome due to adenotonsillar hypertrophy with comorbid conditions, such as growth retardation, poor school performance, enuresis and behavioral problems
- Recurrent throat infection:
  - $\geq$7 episodes in the past year
  - $\geq$5 episodes per year for 2 years
  - $\geq$3 episodes per year for 3 years

Each episode of sore throat must be accompanied by one or more of the following: temperature >101°F (38.3°C), cervical adenopathy, tonsillar exudate, or positive test for GAS.

Other factors that may be considered in children who do not meet the criteria that favor tonsillectomy are:

- Multiple antibiotic allergies/intolerances
- PFAPA (see question 99)
- History of peritonsillar abscess

Baugh RF, Archer SM, Mitchell RM, et al. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg.* 2011;144(1 Suppl):S1–S30.

267. How should children with epiglottitis be managed?

Acute epiglottitis is a medical emergency, and all children should be assumed to have a critical airway (i.e., the potential for imminent occlusion exists). Because of the risk for airway obstruction with agitation of the patient, the patient should be allowed to remain with parents and free from restraint. Examination should be performed as cautiously as possible. Continuous observation, regardless of the setting (e.g., radiology suite), avoidance of supine positioning, and arrangements for admission to an intensive care unit are mandatory. Ideally, the epiglottis is visualized directly in an operating room, and the child is intubated immediately afterward.

268. What are the bacterial causes of epiglottitis?

Previously, more than 90% of cases were caused by Hib. However, because of the routine use of Hib vaccines in infants beginning in 1989 and 1990, the incidence of epiglottitis has decreased dramatically. Pneumococci, staphylococci, streptococci (group A), and nontypeable *H. influenzae* now account for a relatively large percentage of cases.

269. How is epiglottitis distinguished clinically from croup?

See Table 10.6.

Table 10.6 Clinical Distinctions Between Croup and Epiglottitis

	CROUP	EPIGLOTTITIS
Age	Younger (6 mo-3 yr)	Older (3-7 yr)
Onset of stridor	Gradual (24-72 hr)	Rapid (8-12 hr)
Symptoms	Prodromal upper respiratory infection Barking or brassy cough Hoarseness Slightly sore throat	Minimal rhinitis Little coughing Muffled voice Pain in throat
Signs	Mild fever Not toxic Variable distress Harsh inspiratory stridor Expiratory sounds uncommon	High body temperature (>102.2°F [39°C]) Toxic appearance Severe distress; sits upright; may drool Low-pitched inspiratory stridor May have a low-pitched expiratory sound
Radiology	Subglottic narrowing	Edema of epiglottis and aryepiglottic folds (positive thumb sign)

270. What are the criteria for the admission of a child with viral croup?

- Clinical signs of impending respiratory failure:
  - Marked retractions, depressed level of consciousness, cyanosis, hypotonicity, and diminished or absent inspiratory breath sounds
- Laboratory signs of impending respiratory failure:
  - $P_{CO_2} > 45$ mm Hg,
  - $P_{aO_2} < 70$ mm Hg in room air
- Clinical signs of dehydration or inability to tolerate enteral fluids
- Failure of outpatient or emergency room management, such as dexamethasone and inhaled racemic epinephrine, after appropriate monitoring interval
- Historical consideration: high-risk infant with history of subglottic stenosis or prior intubations

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Smith DK, McDermott AJ, Sullivan JF. Croup: diagnosis and management. *Am Fam Physician.* 2018;97(9):575–580.
Bjornson CL, Johnson DW. Croup. *Lancet.* 2008;371:329–339.

271. Are steroids efficacious for the treatment of croup?

The use of corticosteroids (including oral and IM dexamethasone and nebulized budesonide) has been shown to be beneficial in treating croup. In particular, corticosteroid treatment reduces the incidence of intubation and results in more rapid respiratory improvement, including reduction of symptoms of croup at 2 hours after usage compared with placebo. In addition, among patients with mild or moderate croup, corticosteroids appear to reduce the use of nebulized racemic epinephrine, the need for return visits, and the need for hospitalization. Optimal doses are not clearly established. Dosing of dexamethasone is often based on the severity of croup, ranging from mild croup with oral dosing (0.3 to 0.6 mg/kg up to 10 mg) to severe croup with IV or IM dosing (0.6 mg/kg up to 15 mg).

Gates A, Gates M, Vandermeer B, et al. Glucocorticoids for croup in children. *Cochrane Database Syst Rev.* 2018;8:CD001955.
Ortiz-Alvarez O. Acute management of croup in the emergency department. *Paediatr Child Health.* 2017;22(3):166–173.

272. If a child has received racemic epinephrine as a treatment for croup, is hospitalization required?

No. In earlier days, children treated with racemic epinephrine were routinely hospitalized to observe for potential "rebound" mucosal edema and airway obstruction, regardless of how they appeared clinically. However, a number of studies have shown that children who are free of significant stridor or retractions at rest 2 hours after the administration of racemic epinephrine can be safely discharged, provided that adequate follow-up is ensured. In most of these studies, oral or IM dexamethasone (0.6 mg/kg) was also administered.

Bjornson C, Russell K, Vandermeer B, et al. Nebulized epinephrine for croup in children. *Cochrane Database Syst Rev.* 2013;10:CD006619.
Cherry JD. Croup. *N Engl J Med.* 2008;358(4):384–391.

273. Is a cool-mist vaporizer truly of benefit for patients with croup?

Probably not. The usual advice for the home management of croup includes the use of a cool-mist vaporizer. The theory is that the coolness serves as a vasoconstrictor and that the humidified mist serves to thin respiratory secretions. Although this therapy remains time honored, it is largely unproven. A 2006 review of the value of humified air in the treatment of croup found that mild to moderate croup did not improve significantly with the inhalation of humified air. The calming effects of being held by a parent during the mist treatment may have greater impact. It certainly cannot hurt.

Bjornson CL, Johnson DW. Croup in children. *CMAJ.* 2013;185(15):1317–1323.
Cherry JD. Croup. *N Engl J Med.* 2008;358(4):384–391.
Moore M, Little P. Humidified air inhalation for treating croup. *Cochrane Database Sys Rev.* 2006;3:CD002870.

274. What differentiates membranous croup and pseudomembranous croup?

Membranous croup is the historical term for **diphtheria**, and *pseudomembranous croup* is the historical term for **bacterial tracheitis**. Bacterial tracheitis is usually caused by *S. aureus* and may occur after trauma to the neck or trachea or after a viral respiratory tract infection such as croup. The presentation of bacterial tracheitis is similar to that of severe croup or epiglottitis, and consequently a lateral neck radiograph is frequently obtained. In bacterial tracheitis, this study often reveals narrowing of the tracheal lumen as the result of a thick, purulent exudate that can extend into both mainstem bronchi.

Kuo CY, Parikh SR. Bacterial tracheitis. *Pediatr Rev.* 2014;35(11):497–499.
Woodburn, FC. Is membranous croup diphtheria? Read before the Indiana State Medical Society at Indianapolis, May 17, 1894. *JAMA.* 1894;121:776–778.

SINUSITIS

KEY POINTS: SINUSITIS

1. Frontal sinus pneumatization is absent in 1% to 4% of the population.
2. Character of nasal secretions does not distinguish viral from bacterial cause.
3. Early treatment of purulent nasal discharge is a common cause of antibiotic overuse.
4. Compared with adults, sinusitis in children is characterized by persistent nasal symptoms rather than acute fever, headache, and facial pain.
5. Routine imaging to distinguish acute bacterial sinusitis from viral URI is not recommended.

275. When do the sinuses develop during childhood?

The maxillary and ethmoid sinuses are present at birth. Pneumatization of the sphenoid sinuses begins at about 2 to 3 years of age and is usually complete by about age 5. Frontal sinus pneumatization varies considerably, beginning at about 3 to 7 years of age and finishing by age 12 years. Frontal sinus pneumatization is absent in about 1% to 4% of the normal population due to agenesis. About 15% have unilateral frontal sinus hypoplasia.

Adibelli ZH, Songu M, Adibelli H. Paranasal sinus development in children: a magnetic resonance imaging analysis. *Am J Rhinol Allergy.* 2011;25(1):30–35.

276. Does a thick, green nasal discharge on day 2 of a respiratory illness indicate a bacterial sinus infection?

No. The character of nasal secretions (e.g., purulent, discolored, tenacious) does not distinguish viral from bacterial causes. Mucopurulent rhinitis often accompanies the common cold. Early treatment (<7 to 10 days) of purulent nasal discharge is a common cause of antibiotic overuse.

Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics.* 2013;132(1):e262–e280.

277. What is the typical presentation of sinusitis in children?

Unlike adults, who may present with fever and localized pain, children have **persistent nasal symptoms** (anterior or posterior discharge, obstruction, or congestion) without improvement for 10 to 14 days or worsening after 5 to 7 days with or without improvement ("second" or "double sickening") and daytime cough (which may worsen at night). A minority of children may present with a more acute disease accompanied by a temperature of ≥102.2°F (39°C) and a persistent (≥3 days) purulent nasal discharge. These children generally appear ill. Headache and facial pain are uncommon in younger patients with sinusitis but are seen more commonly in older children and teenagers who have had increased sinus pneumatization.

Arora HS. Sinusitis in children. *Pediatr Ann.* 2018;47(10):e396–e401.
Demuri GP, Wald ER. Acute bacterial sinusitis in children. *N Engl J Med.* 2012;367(12):1128–1134.

278. What is the role of sinus imaging in the diagnosis of sinusitis?

Both the AAP and IDSA guidelines discourage *routine* imaging to distinguish acute bacterial sinusitis from viral URI. Abnormal radiographs cannot distinguish bacterial or viral etiologies of sinusitis. Plain radiographs may have findings of diffuse opacification, mucosal swelling, and air–fluid levels. CT scans or MRI may also demonstrate abnormalities such as mucosal thickening or air–fluid levels even in children without complaints of upper respiratory symptoms.

Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics.* 2013;132(1):e262–e280.
Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis.* 2012;54(8):e72–e112.

279. What should be suspected in an adolescent male with a very severe frontal headache in the setting of sinusitis?

- **Intracranial complication** of sinusitis, such as subdural or epidural empyema, venous thrombosis, brain abscess, or meningitis, should be suspected. For unclear reasons, previously healthy adolescent males with frontal sinusitis are noted to have an increased risk for intracranial complications.
- **Orbital complications**, such as subperiosteal abscess, orbital cellulitis, orbital abscess, and cavernous sinus thrombosis, comprise the other major category of complications of acute sinusitis.

DeMuri GP, Wald ER. Complications of acute bacterial sinusitis in children. *Pediatr Infect Dis J.* 2011;30(8):701–702.
Rosenfeld EA, Rowley AH. Infectious intracranial complications of sinusitis, other than meningitis, in children: 12 year review. *Clin Infect Dis.* 1994;18(5):750–754.

280. When should imaging be considered in cases of sinusitis?

A contrast-enhanced CT scan and/or an MRI with contrast is recommended when there is suspicion of orbital or CNS complications of acute bacterial sinusitis. The evidence for one imaging modality over the other is weak, but in general, CT is more readily available; faster (possibly obviating the need for sedation); will better visualize bony complications of the orbit (which are the most common types of complications); and, in most cases, visualizes intracranial pathology. There are case reports of failure of CT to reveal intracranial complications of sinusitis, and so an MRI with contrast may be considered in the case of a negative CT with a high index of suspicion or specific concern for soft tissue complications.

Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics.* 2013;132(1):e262–e280.
Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis.* 2012;54(8):e72–e112.

281. Which organisms are responsible for acute and chronic sinusitis in the pediatric age group?

In **acute, uncomplicated sinusitis**, the etiologic organisms closely parallel those associated with AOM: *S. pneumoniae, H. influenzae,* and *M. catarrhalis*. There is increasing evidence that in the era of the conjugate pneumococcal vaccinations (PCV-7 and PCV-13), β-lactamase–producing strains of *H. influenzae* are supplanting *S. pneumoniae* as the most common organism. In patients with **chronic sinusitis**, the most common pathogens remain *S. pneumoniae, H. influenzae,* and *M. catarrhalis,* along with *S. aureus* and anaerobes. Fungal infection with zygomycosis (mucormycosis) is an important concern in immunosuppressed patients. *P. aeruginosa* or other colonizing gram-negative organisms must always be considered in patients with cystic fibrosis. *S. aureus,* both MRSA and MSSA, is emerging as a pathogen in acute and chronic sinusitis, particularly in cases of complicated disease.

Wald ER, DeMuri GP. Antibiotic recommendations for acute otitis media and acute bacterial sinusitis: conundrum no more. *Pediatr Infect Dis J.* 2018;37(12):1255–1257.

282. What is the management of acute sinusitis?

Antibiotic therapy is designed to target the most common organisms. However, culture data from the postpneumococcal vaccine era is limited because direct sampling from the sinuses is a procedure not commonly done. As noted in the preceding question, there is some evidence that beta-lactamase–producing *H. influenza* may be supplanting *S. pneumoniae* as the most common cause of sinusitis. Pathogens causing sinusitis are typically in parallel with those causing otitis media where this bacteriologic shift has been more readily measurable. Currently, amoxicillin, 45 mg/kg per day, is recommended as first-line therapy for children $\geq$2 years of age with uncomplicated acute bacterial sinusitis. If there is a suspicion based on local epidemiology of resistant *S. pneumoniae,* high-dose (80 to 90 mg/kg per day) amoxicillin may be used. For children $<$2 years of age, children attending day care facilities, or patients who have recently been treated with an antibiotic such as amoxicillin, amoxicillin-clavulanate with 80 to 90 mg/kg per day of the amoxicillin component is recommended. A 10- to 14-day course of therapy is typically advised. Because of the potential shift due to the postpneumococcal conjugate vaccines in the bacteriologic causes of sinusitis with increasing percentages of beta-lactamase–producing pathogens, some experts recommend consideration of regular dose amoxicillin-clavulanate rather than amoxicillin alone as first-line therapy in all cases of uncomplicated acute bacterial sinusitis.

Wald ER, DeMuri GP. Antibiotic recommendations for acute otitis media and acute bacterial sinusitis: conundrum no more. *Pediatr Infect Dis J.* 2018;37(12):1255–1257.

Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics.* 2013;132(1):e262–e280.

Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis.* 2012;54(8):e72–e112.

283. What are the predisposing factors for the development of chronic sinusitis?

- Allergic rhinitis
- Anatomic abnormalities (e.g., polyps, enlarged adenoids)
- Impairment of mucociliary clearance (e.g., cystic fibrosis, primary ciliary dyskinesia)
- Foreign bodies (e.g., nasogastric tube)
- Abnormalities in immune defense (e.g., IgA deficiency)

TUBERCULOSIS

284. How effective is the Bacillus Calmette-Guerin (BCG) vaccination?

The BCG vaccines are among the most widely used in the world and are also perhaps the most controversial. The difficulties stem from the marked variation in reported efficacy of BCG against *Mycobacterium tuberculosis* and *Mycobacterium leprae* infections. Depending on the population studied, efficacy against leprosy has ranged from 20% to 60% in prospective trials. The efficacy against tuberculosis has ranged from 0% to 80%. The highest protective effect is seen against meningeal and miliary tuberculosis in young children. In areas of high endemicity or in populations where morbidity and mortality are significant, the vaccine is used.

The vaccines were derived from a strain of *Mycobacterium bovis* in 1906 and were subsequently dispersed to several laboratories around the world, where they were propagated under nonstandardized conditions. Hence, the vaccines in use today cannot be considered homogeneous. This may explain the observed variation in efficacy.

285. What are the steps in screening for *M. tuberculosis*?

- **Assessment of risk**: Primary care providers should assess patient risk factors for tuberculosis at the first visit, every 6 months for the first year of life, and then annually. Risk factors include children with household contacts with confirmed or suspected tuberculosis, children emigrating from countries with endemic tuberculosis, or children who have traveled to endemic countries and have had significant contact with persons at risk for tuberculosis. A validated screening questionnaire is available from the AAP.
- **For those children with a positive risk factor screen**, the most common diagnostic test remains the standard-strength purified protein derivative (PPD) (Mantoux test) in children $<$2 years and/or without BCG vaccination; this contains 5 tuberculin units (TU) of PPD and is injected intradermally. An interferon gamma release assay can be used after the age of 2 years.

American Academy of Pediatrics. Tuberculosis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:833–837.

286. How is the Mantoux test interpreted in the context of clinical signs and symptoms and epidemiologic risk factors, such as a known exposure?

Positive tests are defined as follows:

Palpable induration of ≥5 mm

- Children in close contact with confirmed or suspected cases of tuberculosis
- Children with radiographic or clinical evidence of tubercular disease
- Children receiving immunosuppressive therapy
- Children with immunodeficiency disorders, including HIV infection

Palpable induration of ≥10 mm

- Children <4 years
- Children with Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition
- Children born in high-prevalence regions of the world, whose parents were born in such areas, or who have traveled to such areas
- Children frequently exposed to adults who are infected with HIV, homeless, incarcerated, illicit drug users, or migrant farm workers

Palpable induration of ≥15 mm

- Children 4 years or older with no risk factors

American Academy of Pediatrics, Tuberculosis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:830.

287. What are the reasons for a false-negative tuberculin skin test (TST)?

About 10% to 40% of immunologically normal patients with culture-documented disease will have an initial TST that is negative. Reasons include:

- Testing during the incubation period (2 to 10 weeks)
- Young age
- Problems with the administration technique
- Severe systemic tuberculosis infection (miliary or meningitis)
- Concurrent infection: Measles, varicella, influenza, HIV, EBV, *Mycoplasma*, mumps, rubella

Children who are on immunosuppressive medications, who suffer from malnutrition, or who have an immunodeficiency may also have false-negative results.

288. How does BCG immunization influence tuberculosis skin testing?

Generally, the interpretation of PPD tests is the same in BCG recipients as it is in nonvaccinated children. If positive, consideration should be given to several factors when deciding who should receive antituberculous therapy. These factors include time since BCG immunization, number of doses received, prevalence of tuberculosis in the country of origin, contacts in the United States, and radiographic findings. As discussed in the next question, interferon-γ release assay (IGRA) testing may be helpful in children who have received the BCG vaccine.

289. What is the role of IGRAs in the diagnosis of tuberculosis in children?

IGRAs rely on interferon-γ produced by lymphocytes sensitized by antigens specific to *M. tuberculosis*. These antigens are not found in the BCG vaccine or in nontuberculous mycobacteria, such as *M. avium* infection. A whole-blood ELISA can measure the interferon-γ concentration after incubation with antigen. IGRAs are preferable to TST in the following circumstances:

- Children ≥2 years of age who have received the BCG vaccine
- Children ≥2 years of age who are unlikely to return for TST reading

In children <2 years of age, there are limited data on the validity of the test.

American Academy of Pediatrics. Tuberculosis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:834.

290. How are IGRA results interpreted?

In general, the sensitivity of IGRAs is similar to TSTs in children ≥2 years. The specificity is higher because antigens found in the BCG vaccine and some nontuberculous mycobacteria do not react with the assay.

- A child with a positive IGRA should be considered infected with *M. tuberculosis*.
- A child with a negative IGRA result cannot be interpreted as definitively free of infection.
- Indeterminate IGRA results do not exclude tuberculosis infection.
  - In the case of an indeterminate test, a repeat IGRA should be performed.
  - If the repeat is still indeterminate, a TST may be performed.

291. How should a patient with a positive TST or IGRA be evaluated?

- **History** should search for clues that are suggestive of active infection, such as recurrent fevers, weight loss, adenopathy, or cough. A history of recurrent infections in the patient or a family member may be suggestive of HIV infection, which is a risk factor for infection with *M. tuberculosis*. Information from previous tuberculin skin testing is invaluable. Epidemiologic information includes an evaluation of possible exposure to tuberculosis. A family history is obtained, including questions pertaining to chronic cough or weight loss in a family member or other contact. Travel history and current living arrangements should be elucidated. If the patient has immigrated to North America, a history of BCG vaccination should be ascertained.
- **Physical examination** should focus on pulmonary, lymphatic, and abdominal systems. Examination should corroborate a history of BCG vaccination.
- **Laboratory evaluation**, including a chest radiograph with a lateral film, is the next stage. Family members and close contacts should undergo testing. In certain circumstances, chest radiographs should be performed on the child's contacts. If any of the preceding evaluations suggest active infection, sputum, gastric aspirates, and other appropriate specimens (e.g., lymph node tissue) should be obtained for mycobacterial culture and NAAT.

292. How common is HIV and tuberculosis coinfection?

Approximately 1 million people worldwide are coinfected with HIV and tuberculosis. In the United States, it is estimated that 10% of patients with active tuberculosis also have HIV. There is a 5% to 15% annual risk for acquiring tuberculosis in HIV-positive populations, and the risk for progression from latent to active disease is much greater. Children with HIV infection are considered at high risk for contracting tuberculosis, and annual TST beginning at 3 to 12 months of age (or at the time of HIV diagnosis) is recommended. Children who are diagnosed with tuberculosis should be tested for HIV infection.

Méndez-Samperio P. Diagnosis of tuberculosis in HIV co-infected individuals: current status, challenges and opportunities for the future. *Scan J Immunol.* 2017;86(2):76–82.

Zumla A, Ravliglione M, Hafner R, et al. Tuberculosis. *N Engl J Med.* 2013;368(8):745–755.

293. What is latent tuberculosis infection (LTBI), and why is it treated?

A patient with a positive TST or IGRA who has no clinical or radiographic abnormalities suggesting tuberculosis is thought to have *LTBI*. If a patient has never received antituberculous medication and has not had a known exposure to a person with isoniazid-resistant tuberculosis, treatment for LTBI has an efficacy near 100% in preventing progression to disease.

294. In a younger child suspected of having tuberculosis, what is the utility of gastric aspirates?

In infants and young children, a cough may be absent or nonproductive. Hypertonic saline may be used in many children to successfully induce sputum for diagnosis. If this is not possible, gastric aspirates may be used as a source for the culture or PCR identification of *Mycobacteria*. The aspirate should be obtained early in the morning as the child awakens to sample the overnight accumulation of respiratory secretions. The first day's collection generally has the highest yield.

295. What is the role of NAAT in the diagnosis of tuberculosis?

NAAT/PCR-based technology is commercially available for the detection of tuberculosis. The Xpert MTB/RIF assay also tests for rifampicin resistance. A 2019 Cochrane review indicated this assay had an overall sensitivity of 85% and a specificity of 98% in adults. Additionally, it has been shown to have a sensitivity of 67% in patients who are acid-fast bacilli (AFB) smear negative. Additional studies have shown a sensitivity of 80% in extrapulmonary specimens and a CSF sensitivity and specificity of 64% and 98%, respectively. This is a hopeful development for timely diagnosis, given the limitation of obtaining cultures in children, as well as the generally low mycobacterial burden in many specimens in children.

Home DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev.* 2019;6:CD009593.

296. How do the manifestations of active pulmonary tuberculosis on chest radiograph differ between adults and children?

Adults and *adolescents* more commonly present with **cavitary disease** and **pleural effusions**. The hallmark of pulmonary tuberculosis in *children* has classically been described as **hilar adenopathy** (Fig. 10.17). Both adults and children, but more commonly adults, may present with lobar infiltrates. Classically, the right upper lobe has been implicated because the right mainstem bronchus provides the most direct route for inhaled *Mycobacterium*. A caveat is that tuberculosis may be heterogeneous in radiographic appearance and should never be "ruled out" given appropriate clinical suspicion based on x-ray alone, in either children or adults.

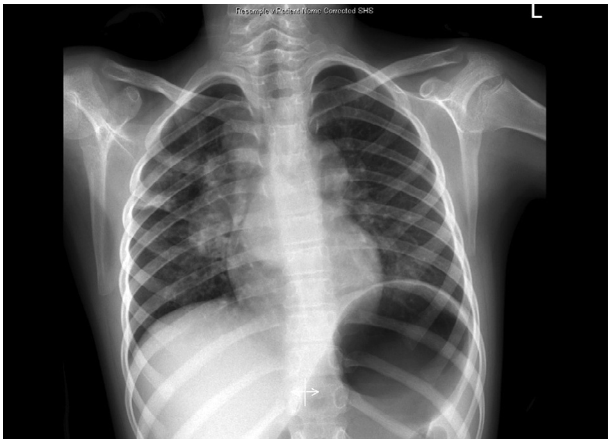

Fig. 10.17 Chest x-ray with hilar adenopathy in a child with tuberculosis. (From Ki HP, Shingadia D. Tuberculosis in children. *Paediatr Child Health.* 2017;27(3):110.)

Janner D. *A Guide to Pediatric Infectious Disease*. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:126.
Agrons GA, Markowitz RI, Kramer SS. Pulmonary tuberculosis in children. *Semin Roentgenol.* 1993;28(2):158–172.

297. How are children with active pulmonary tuberculosis treated?

Recommendations for the treatment of active tuberculosis in children have evolved over the past several years. Previously, therapy for at least 9 months was suggested for uncomplicated pulmonary disease. Studies in adults and children have demonstrated that 6 months of combined antituberculous therapy (short-course therapy) is as effective as 9 months of therapy. To date, the combined results of multiple studies in pediatric patients have demonstrated the efficacy of 6 months of therapy to be more than 95%. The current standard regimen for active pulmonary tuberculosis in children consists of 2 months of daily isoniazid, rifampin, and pyrazinamide followed by 4 months of isoniazid and rifampin (daily or twice weekly). If drug resistance is a concern, either ethambutol or streptomycin is added to the initial three-drug regimen until drug susceptibilities are determined.

American Academy of Pediatrics. Tuberculosis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:838–847.
Perez-Velez CM, Marais BJ: Tuberculosis in children. *N Engl J Med.* 2012;367(4):348–361.

298. Why are multiple antibiotics used for the treatment of tuberculosis?

Compared with a patient with a positive test but no disease, two features of *M. tuberculosis* make the organism difficult to eradicate after infection has been established. First, *Mycobacteria* replicate slowly and may remain dormant for prolonged periods, but they are susceptible to drugs only during active replication. Second, drug-resistant organisms exist naturally within a large population, even before the initiation of therapy. These features render the organism—when it is present in significant numbers—extremely difficult to eradicate with a single agent.

299. What are the signs of tuberculous meningitis?

Tuberculous meningitis is a tragic form of the disease. It has a peak incidence in young children (<5 years of age) and is the most common extrapulmonary manifestation of tuberculosis in this age group, especially in HIV-coinfected children. The symptoms are insidious and nonspecific. These include decreased level of consciousness and lethargy, cranial nerve palsies, poor weight gain, and low-grade fever that persists, typically for >5 days. It can be difficult to clinically differentiate from other forms of meningitis once it is recognized because CSF AFB smears and cultures are often negative. Mortality approaches 30%, and >50% of survivors have neurodevelopmental sequelae.

Mai NT, Thwaites GE. Recent advances in the diagnosis and treatment of tuberculous meningitis. *Curr Opin Infect Dis.* 2017;30(1):123–128.
Chiang SS, Khan FA, Milstein MB. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2014;14(10):947–957.

300. What is the importance of directly observed therapy (DOT) in the treatment of tuberculosis?

DOT, administration of medication by a third party (either a health care professional or a trained unrelated individual), has been found to be a valuable approach to the treatment of children and adolescents with tuberculosis. Failure to properly take chronic medications increases the likelihood of relapse and the development of resistance. DOT increases adherence and thus lowers rates of relapse, treatment failures, and drug resistance.

301. Why is pyridoxine supplementation given to patients who are receiving isoniazid?

Isoniazid interferes with pyridoxine metabolism and may result in peripheral neuritis or convulsions. The administration of pyridoxine is generally not necessary for children who have a normal diet because they have adequate stores of this vitamin. Children and adolescents with diets deficient in milk or meat, exclusively breastfed infants, symptomatic HIV-infected children, and pregnant women should receive pyridoxine supplementation during isoniazid therapy.

302. Why do children with tuberculosis rarely infect other children?

Tuberculosis is transmitted by infected droplets of mucus that become airborne when an individual coughs or sneezes. Compared with adults, children with tuberculosis have several factors that minimize their contagiousness:

- Low density of organisms in sputum
- Lack of cavitations or extensive infiltrates on chest radiograph
- Lower frequency of cough
- Lower volume and higher viscosity of sputum
- Shorter duration of respiratory symptoms

Starke JR. Childhood tuberculosis during the 1990s. *Pediatr Rev.* 1992;13(9):343–353.

303. In addition to tuberculosis, what other airborne microbes can cause respiratory disease?

See Table 10.7.

Table 10.7 Airborne Microbial Diseases

DISEASE	AIRBORNE SOURCE
Aspergillosis	Conidia spores from decaying vegetation and soil
Brucellosis	Aerosolized from carcasses of domestic and wild animals
Chickenpox	Aerosolized from respiratory secretions
Coccidioidomycosis	Arthroconidia from soil and dust
Cryptococcosis	Aerosolized from bird droppings
Histoplasmosis	Conidia spores from bat or bird droppings
Legionnaires disease	Aerosolized contaminated water, especially from air-conditioning cooling towers
Measles	Aerosolized respiratory secretions
Mucormycosis	Spores from soil
Psittacosis	*Chlamydia psittaci* from birds
Q fever	*Coxiella burnetii* from a variety of farm and other animals
Tularemia	Aerosolized from multiple wild animals, especially rabbits

304. Which famous U.S. first lady died of tuberculosis?

Eleanor Roosevelt, for whom immunosuppressive therapy for aplastic anemia activated dormant tuberculosis, died of the disease. Historically, tuberculosis has been called "consumption" (as the disease "consumed" the individual with drastic weight loss). Other noteworthy historical and literary figures who died from tuberculosis include Thomas Wolfe, George Orwell, Fredrick Chopin, Anton Chekov, and the entire Brontë family (Maria, Elizabeth, Charlotte, Emily, Anne, and brother Branwell).

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CHAPTER 11

NEONATOLOGY

Kathleen G. Brennan, MD, MS and Tina A. Leone, MD

DELIVERY ROOM ISSUES

1. When should the umbilical cord be clamped after birth?

Obstetric and midwifery practice has varied in the timing of umbilical cord clamping over the last 50 years from immediately clamping the cord after birth to clamping when the cord stops pulsating. Immediate cord clamping became common practice as a method aimed at preventing postpartum hemorrhage. However, this practice prevents the natural transfer of fetoplacental blood into the newborn infant once the uterus begins contracting and the infant begins breathing. Several studies have evaluated immediate cord clamping compared with many different time frames for "delayed" clamping. In preterm infants, delayed cord clamping (at least 30 to 60 seconds) has been shown to improve the hemodynamic transition after birth. Infants have less bradycardia after birth, less hypotension, receive fewer vasoactive medications, have lower rates of intraventricular hemorrhage (IVH), and exhibit a lower mortality. In term infants, delayed cord clamping increases hemoglobin levels at birth and improves iron stores in the first few months of life. Delayed cord clamping for 30 to 60 seconds after birth is now recommended by the American College of Obstetrics and Gynecology (ACOG) for vigorous preterm and term infants.

Fogarty M, Osborn DA, Askie L, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2018;218(1):1–18.

Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Committee Opinion No. 684: delayed umbilical cord clamping after birth. *Obstet Gynecol.* 2017;129(1):e5–e10.

2. How long has meconium been present in the amniotic fluid if an infant has evidence of meconium staining?

Gross staining of the infant is a surface phenomenon that is proportional to the length of exposure and meconium concentration. With heavy meconium, staining of the umbilical cord begins in as little as 15 minutes; with light meconium, it occurs after 1 hour. Yellow staining of the newborn's toenails requires 4 to 6 hours. Yellow staining of the vernix caseosa takes about 12 to 14 hours.

Miller PW, Coen RW, Benirschke K. Dating the time interval from meconium passage to birth. *Obstet Gynecol.* 1985;66(4):459–462.

3. Is meconium staining a good marker for neonatal asphyxia?

No. Because 10% to 20% of all deliveries have in utero passage of meconium, meconium staining alone is not a good marker for neonatal asphyxia.

4. During asphyxia, how is primary apnea distinguished from secondary apnea?

A regular sequence of events occurs when an infant is asphyxiated. Initially, gasping respiratory efforts increase in depth and frequency for up to 3 minutes, and this is followed by cessation of breathing *(primary apnea)*. If stimulation is provided during the period of primary apnea, respiratory function spontaneously returns. If asphyxia continues, gasping then resumes for a variable period, terminating with the "last gasp" and followed by secondary apnea. During *secondary apnea,* the only way to restore respiratory function is with positive-pressure ventilation (PPV). Thus a linear relationship exists between the duration of asphyxia and the recovery of respiratory function after resuscitation. The longer the artificial ventilation is delayed after the last gasp, the longer it will take to resuscitate the infant. However, clinically, the two conditions may be indistinguishable.

5. How should apnea be managed in the delivery room?

Although there are a variety of causes for apnea in the delivery room, the most concerning is severe acidosis. Although some infants may begin breathing spontaneously in response to tactile stimulation, those with severe acidosis will usually require assisted ventilation to begin breathing spontaneously. An additional sign of acidosis is bradycardia. Therefore any infant who has persistent bradycardia (a heart rate $<$100 beats per minute) or apnea that does not quickly respond to tactile stimulation should be treated with assisted ventilation. If the apnea does not improve with assisted ventilation provided via facemask, the infant will most likely require endotracheal intubation for continued respiratory support.

6. What are the clinical signs of adequate ventilation?

During resuscitation, assessment of the quality of ventilation involves determining whether air is able to enter and exit the lungs. This is seen clinically by observing the chest rise with each inflation **and** by noting clinical improvement, such as an increasing heart rate or onset of spontaneous respiratory effort. It is also possible to use an end tidal carbon dioxide detector with the facemask to visually see that gas exchange is occurring with each breath.

When ventilation is not adequate, the clinician must make adjustments to deliver breaths more effectively. The American Academy of Pediatrics/American Heart Association (AAP/AHA) Neonatal Resuscitation Program (NRP) suggests remembering different adjustments that should be addressed by the mnemonic: ***MR SOPA***

M = **M**ask adjustment
R = **R**epositioning
S = **S**uctioning
O = **O**pen the mouth
P = Increase the **P**ressure
A = Alternate **A**irway

Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016:82–85.

Leone TA, Lange A, Rich W, Finer NN. Disposable colorimetric carbon dioxide detector use as an indicator of a patent airway during non-invasive mask ventilation. *Pediatrics.* 2006;118(1):e202–e204.

7. What is a T-piece resuscitator?

A T-piece resuscitator is a device that uses airflow through a circuit that includes a valve that remains partially occluded, allowing administration of positive end-expiratory pressure (PEEP). The operator provides assisted breaths with a set peak inspiratory pressure (PIP) by completely occluding the valve with a finger. The benefits of this device are that it provides the most consistent levels of pressure during assisted ventilation and it can successfully provide PEEP or continuous positive airway pressure (CPAP) if needed. The main drawback to the device is that the operator must intentionally increase the set pressure by turning a knob on the unit. An operator working alone may not be able to easily accomplish increasing the pressure with this device.

Bennett S, Finer NN, Rich W, Vaucher Y. A comparison of three neonatal resuscitation devices. *Resuscitation.* 2005;67(1):113–118.

8. How does one estimate the size of the endotracheal tube required for resuscitation?

See Table 11.1.

Table 11.1 Endotracheal Tubes Needed for Resuscitation

TUBE SIZE (INTERNAL DIAMETER IN MM)	WEIGHT (G)	GESTATIONAL AGE (WK)
2.5	<1000	<28
3	1001-2000	28-34
3.5	2001-3000	34-38
3.5-4.0	>3000	>38

Data from Hertz D. Principles of neonatal resuscitation. In Polin RA, Yoder MC, Burg FD, eds. *Workbook in Practical Neonatology.* 3rd ed. Philadelphia, PA: W.B. Saunders; 2001:13.

9. When should epinephrine be given during resuscitation in the delivery room?

If an infant's heart rate remains < 60 beats per minute despite adequate PPV provided via advanced airway for at least 30 seconds and another 60 seconds of chest compressions (both with 100% oxygen), epinephrine is indicated. Intravenous (IV) or intraosseous epinephrine is preferred over endotracheal epinephrine. Endotracheal use is less effective due to poorer absorption. The recommended IV/intraosseous dose is 0.1 to 0.3 mL/kg of a 1:10,000 concentration (0.1 mg/mL) given rapidly. If given endotracheally, a larger dose of 0.5 to 1 mL/kg should be considered.

Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016:187, 203.

10. When should a laryngeal mask airway (LMA) be used in neonatal resuscitation?

The LMA fits over the laryngeal inlet and may be used to effect ventilation when intubation is not feasible or is unsuccessful. The LMA should be considered when (1) anomalies of the lip, mouth, or palate make it impossible to achieve a good seal with the bag and mask, and (2) anomalies of the mouth, tongue, pharynx, mandible, or neck make visualization of the larynx with a laryngoscope impossible. Placement of the LMA does not require visualization and may be used to temporize while measures are taken to establish a more stable airway (Fig. 11.1).

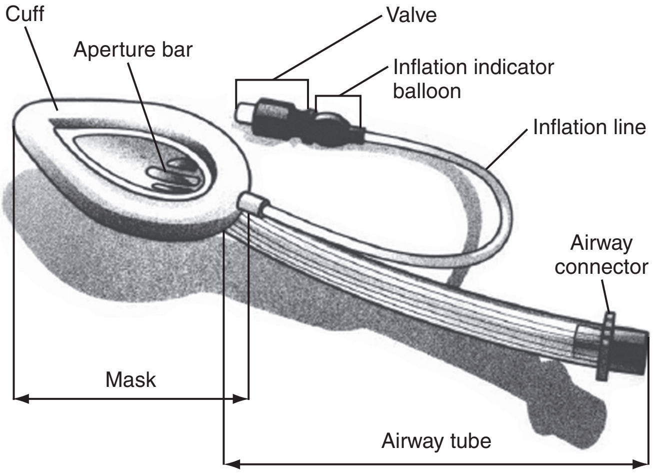

Fig. 11.1 Laryngeal mask airway. (From Asensio JA, Trunkey DD, eds. *Current Therapy of Trauma and Surgical Critical Care*. Philadelphia, PA: Mosby; 2008:59.)

11. What is the role for CO_2 detectors in neonatal resuscitation?

After intubation, visualization of passage of the tube through the vocal cords, auscultation of breath sounds, and observation of chest movement are often used to ensure proper placement of the endotracheal tube in the trachea. However, these signs may be misleading and must be confirmed by rapid improvement in heart rate and detection of CO_2 after a few positive-pressure breaths. CO_2 detectors are available as either colorimetric devices or capnographs giving numeric CO_2 levels, with the former type most commonly used. Beware, however, that patients with very low cardiac output, such as those in cardiac arrest, may have markedly diminished pulmonary blood flow, resulting in failure to detect CO_2 despite tracheal placement of the endotracheal tube.

12. What techniques are available to keep preterm infants warm in the delivery room?

Preterm infants will achieve a higher admission temperature and will have a lower incidence of hypothermia if a plastic bag or wrap is used for temperature control immediately after delivery. Immediately after birth, infants can rapidly lose heat to the environment by evaporation (wet skin), conduction (cool blankets), convection (breezes), and radiation (cool environmental temperature). When preterm infants are treated with standard warming methods used for term infants, the incidence admission temperatures <35°C can be as high as 50%. Several studies have shown that placing plastic around preterm babies (<29 weeks) immediately after birth without drying the skin (excluding the head) leads to higher admission temperatures and less frequent hypothermia. Other interventions to maintain temperature in preterm infants include use of chemical heating mattresses, increasing the temperature of the delivery room, and use of a servo-controlled radiant warmer.

McCall EM, Alderdice F, Halliday HL, et al. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. *Cochrane Database Syst Rev.* 2018;2:CD004210.

13. What amount of oxygen is recommended for neonatal resuscitation?

The NRP recommends use of 21% O_2 (room air) when PPV is required in the resuscitation of *full-term infants*. The partial pressure of O_2 in the placenta is $\approx$50 mm Hg; room air is $\approx$150 mm Hg (21% × 760 mm Hg, the atmospheric pressure). Therefore compared with fetal life, room air increases the delivery of oxygen 3-fold. Evidence from randomized clinical trials shows that using 21% O_2 is just as effective as 100% O_2 and leads to a significant reduction in mortality rates. Therefore current recommendations are to start with 21% O_2 but to increase the inspired oxygen concentration to 100% if the infant has a heart rate <60 beats per minute or is receiving chest compressions. Additionally, the oxygen concentration should be increased if the oxygen saturation values do not reach recommended values over the first 10 minutes of life (see later). Most of the studies from which those recommendations are based enrolled infants $\geq$35 weeks' gestation. Relatively few studies enrolled infants <28 weeks' gestation in clinical trials. In the case of *preterm infants <35 weeks' gestation*, who are vulnerable to hyperoxic injury but are likely to need supplemental oxygen due to lung immaturity, the best initial oxygen concentration for resuscitation is still unknown. For these premature infants, the NRP currently recommends starting with 21% to 30% O_2 and adjusting the oxygen concentration to achieve normal oxygen saturation values. In infants <28 weeks' gestation, we recommend using 30% oxygen and weaning the inspired oxygen concentration if saturation values exceed 95%.

Welsford M, Nishiyama C, Shortt C, et al. Initial oxygen use for preterm newborn resuscitation: a systematic review with meta-analysis. *Pediatrics.* 2019;143(1):e20181828.

Welsford M, Nishiyama C, Shortt C, et al. Room air for initiating term newborn resuscitation: a systematic review with meta-analysis. *Pediatrics.* 2019;143(1):e20181825.

Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016:77.

14. What are normal oxygen saturations (Spo$_2$) values over the first 10 minutes of life?

See Fig. 11.2.

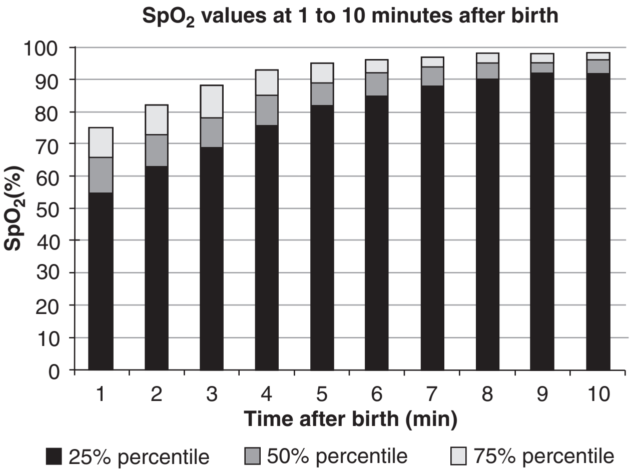

Fig. 11.2 Spo$_2$ values at each minute from 1 to 10 minutes of life.

15. What bone is the most frequently fractured *during delivery* in the newborn?

The **clavicle**. This injury, which stems from excessive traction during delivery, generally results in a greenstick fracture (Fig. 11.3). The second most commonly fractured bone in the neonate is the *humerus,* which can occur from rotation or hypertension of the upper extremity during birth.

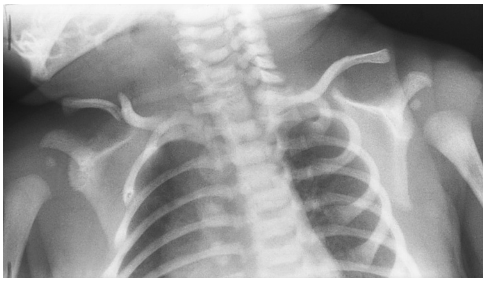

Fig. 11.3 Radiograph of right clavicular fracture. (From Clark DA. *Atlas of Neonatology*. Philadelphia, PA: W.B. Saunders; 2000:8.)

16. Who was Virginia Apgar, and how does one remember her score?

Virginia Apgar, an anesthesiologist at Columbia Presbyterian Medical Center in New York City, introduced the Apgar scoring system in 1953 to assess the newborn infant's response to the stress of labor and delivery. A mnemonic to help remember the components uses the letters of her last name:

- **A**ppearance (pink, mottled, or blue)
- **P**ulse (>100, <100, or 0 beats per minute)
- **G**rimace (response to suctioning of the nose and mouth)
- **A**ctivity (flexed arms and legs, extended limbs, or limp)
- **R**espiratory effort (crying, gasping, or no respiratory activity)

Each category is assigned a rating of 0, 1, or 2 points, with a total score of 10 indicating the best possible condition.

17. Is a low Apgar score alone sufficient to diagnose a neonate as asphyxiated?

No. It is not acceptable to label an infant as asphyxiated simply because of a low Apgar score. Apgar scores reflect the status of a newborn infant immediately after birth, as well as the response to resuscitation, if needed. Apgar scores are not predictive of individual mortality or neurologic outcome. Asphyxiated infants demonstrate a constellation of findings, including multiorgan system dysfunction and signs referable to the central nervous system (CNS). In addition, asphyxiated neonates typically have a profound metabolic acidosis. The cardinal features of hypoxic-ischemic encephalopathy include seizures, alterations of consciousness, and abnormalities of tone. Disorders of reflexes, respiratory pattern, oculovestibular responses, and autonomic function are less significant components of this entity.

American Academy of Pediatrics Committee on Fetus and Newborn, American Academy of Obstetricians and Gynecologists and Committee on Obstetric Practice. The Apgar score. *Pediatrics.* 2015;136(4):819–822.

Leuthner SR, Das U. Low Apgar scores and the definition of birth asphyxia. *Pediatr Clin North Am.* 2004;51:737–745.

18. When should neonatal resuscitation be stopped?

Although each case should be considered individually, the discontinuation of assisted ventilation and other resuscitative efforts is generally appropriate for an infant with an Apgar score of 0 (and thus no undetectable heart rate) after 10 minutes despite adequate resuscitative measures. Current data suggest that asystole for $>$10 minutes is highly unlikely to result in survival or survival without severe disability.

Wyckoff MH, Aziz K, Escobedo MB, et al. Part 13: Neonatal resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132(Suppl 2):S204.

FETAL AND MATERNAL ISSUES

19. What is the most accurate method of pregnancy dating?

A **first-trimester ultrasound** is the most accurate method of pregnancy dating with a margin of error of 5 to 7 days. Ultrasound measurements in the second trimester provide a gestational age with a margin of error of 7 to 14 days. In the third trimester the margin of error for dating the pregnancy ranges between 21 and 30 days.

Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Committee Opinion No. 700: method for estimating due date. *Obstet Gynecol.* 2017;129(5):e150–e154.

20. What is the first bone in the human fetus to ossify?

The **clavicle**. In the long bones, the process of ossification occurs in the primary centers of ossification in the diaphysis during the embryonic period of fetal development. Although the femora are the first long bones to show traces of ossification, the clavicles, which develop initially by intramembranous ossification, begin to ossify before any other bones in the body.

21. What external characteristics are useful for estimating gestational age?

See Table 11.2.

Table 11.2 External Gestational Age Characteristics

EXTERNAL CHARACTERISTICS	*Gestational Age*			
	28 WEEKS	**32 WEEKS**	**36 WEEKS**	**40 WEEKS**
Ear cartilage	Pinna soft, remains folded	Pinna slightly harder but remains folded	Pinna harder, springs back	Pinna firm, stands erect from head
Breast tissue	None	None	1-2-mm nodule	6-7-mm nodule
Male genitalia	Testes undescended, smooth scrotum	Testes in inguinal canal, few scrotal rugae	Testes high in scrotum, more scrotal rugae	Testes descended, pendulous, scrotum covered with rugae
Female genitalia	Prominent clitoris, small widely separated labia	Prominent clitoris, larger separated labia	Clitoris less prominent, labia majora covers labia minora	Clitoris covered by labia majora
Plantar surface	Smooth	1-2 anterior creases	2-3 anterior creases	Creases cover sole

From Volpe JJ. *Neurology of the Newborn.* 5th ed. Philadelphia, PA: W.B. Saunders; 2008:122.

22. What are the increased risks of twin pregnancies?

- Premature delivery
- Intrauterine growth restriction (IUGR) and/or discordant growth (which may occur in up to one-third of twin pregnancies)
- Increased perinatal mortality, especially for premature, monozygotic, and discordant twins
- Spontaneous abortion
- Birth asphyxia
- Fetal malposition
- Placental abnormalities (abruptio placentae, placenta previa)
- Polyhydramnios

23. Why are monozygotic twins considered higher risk than dizygotic twins?

- *Monozygotic twins* (identical twins) arise from the division of a single fertilized egg. Depending on the timing of the division of the single ovum into separate embryos, the amniotic and chorionic membranes can either be shared (if division occurs $>$8 days after fertilization), separate (if division occurs $<$72 hours after fertilization), or mixed (separate amnion, shared chorion if division occurs 4 to 8 days after fertilization). Sharing of the chorion and/or amnion is associated with potential problems of vascular anastomoses (and possible twin–twin transfusions), cord entanglements, and congenital anomalies. These problems increase the risk for IUGR and perinatal death.
- *Dizygotic twins,* however, result from two separately fertilized ova and, as such, usually have a separate amnion and chorion.

24. What are the known benefits of antenatal corticosteroids, and when are they indicated?

In multiple studies with large numbers of subjects, antenatal corticosteroid therapy has been shown to significantly improve newborn outcomes with decreased rates of neonatal mortality, respiratory distress syndrome (RDS), IVH, and necrotizing enterocolitis (NEC).

Antenatal corticosteroid treatment should be given to pregnant women with fetuses between 24 and 34 weeks at risk for delivery within the next week. Before 24 weeks, the decision to provide steroid treatment should be individualized based on the plans for intervention after delivery at that gestational age. Beyond 34 weeks' gestation (i.e., late preterm infants), there remains uncertainty about the benefits and long-term effects of antenatal corticosteroid therapy, although one large randomized study found administration of betamethasone to women at risk for late preterm delivery significantly reduced the rate of neonatal respiratory complications.

Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev.* 2017;3:CD004454.
Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Committee Opinion No. 713: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol.* 2017;130(2):e102–e109.
Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med.* 2016;374(14):1311–1320.

25. What are the potential fetal and postnatal effects associated with diabetes during pregnancy?

The most significant problem faced by infants of diabetic mothers is increased perinatal mortality. Other effects include an increased risk for congenital malformations (commonly cardiac and/or neurologic) disturbances in fetal growth (large for gestational age or small for gestational age [SGA]), as well as postnatal physiologic and adaptational problems including hypoglycemia, hypocalcemia, polycythemia, RDS, and hypertrophic cardiomyopathy. Poor glycemic control is associated with most of the complications of diabetes during pregnancy but does not explain all possible problems.

26. What interventions are indicated in future pregnancies after a mother delivers a preterm infant?

Women who have delivered preterm infants have an approximate 20% to 30% chance of delivering a preterm infant in subsequent pregnancies. These women are therefore considered high risk and should be monitored closely in future pregnancies.

Therapy with progesterone during subsequent pregnancies has been shown to decrease the rate of subsequent preterm birth and decrease the risk for perinatal and neonatal mortality. Current guidelines by the Society for Maternal-Fetal Medicine recommend weekly intramuscular injections with 17-alphahydroxyprogesterone caproate starting at 16 to 20 weeks and continuing through 36 weeks.

Society for Maternal-Fetal Medicine Publications Committee. The choice of progesterone for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth. *Am J Obstet Gynecol.* 2017;216(3):B11–B13.
Dodd JM, Jones L, Flenady V, et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev.* 2013;7:CD004947.

27. How is hypertension in pregnancy classified?

Hypertension in pregnancy is divided into four categories:

- **Preeclampsia-eclampsia**: hypertension with systemic manifestations, including proteinuria, thrombocytopenia, impaired liver function, and newly developed renal insufficiency

- **Chronic hypertension**: hypertension before pregnancy
- **Chronic hypertension with superimposed preeclampsia**
- **Gestational hypertension**: elevated blood pressure without other systemic findings

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ACOG Practice Bulletin No. 202 Summary. Gestational hypertension and preeclampsia. *Obstet Gynecol.* 2019;133(1):211–214.

28. What are the clinical consequences for the fetus from maternal preeclampsia?

Fetal effects of preeclampsia that are identifiable after birth include:

- **IUGR:** Preeclampsia is the most common cause of IUGR in infants without anomalies.
- **Preterm birth**: Preterm delivery is indicated when preeclampsia is severe and may be considered at lower levels of severity at the discretion of the obstetrician.
- **Hypoglycemia**: Hypoglycemia occurs as a consequence of poor intrauterine growth and reduced glycogen stores.
- **Neutropenia**: Neutropenia can be severe but is usually self-limited.
- **Thrombocytopenia**: Thrombocytopenia is usually mild and self-limited.
- **Morbidities associated with prematurity**: Preterm infants born after preeclampsia have morbidities similar to other premature infants. However, there may be a somewhat greater incidence of bronchopulmonary dysplasia (BPD) and neurodevelopmental impairment (NDI) compared with other infants of similar gestational ages.

Backes CH, Markham K, Moorehead P, et al. Maternal preeclampsia and neonatal outcomes. *J Pregnancy.* 2011;2011:214365.

GASTROINTESTINAL ISSUES

29. When does the newborn infant's stomach begin to secrete acid?

In the first hours of life. The pH of gastric fluid in newborns is usually neutral or slightly alkaline in the first hours of life and decreases shortly thereafter. In term infants, pH values are <3 by 6 to 8 hours of age and then increase again during the second week of life. Preterm infants frequently have lower gastric acid production than term infants, and very preterm infants may demonstrate a slightly higher gastric pH depending on the degree of prematurity.

30. When is meconium usually passed after birth?

Most infants pass some meconium during the first 12 hours of life. Overall, 99% of term infants and 95% of premature infants pass meconium by 48 hours of life. However, the smallest of premature infants may have delayed passage of meconium as a result of the relative immaturity of rectal sphincteric reflexes. A term newborn who does not pass stool within 48 hours of life should be evaluated for Hirschsprung disease.

31. How is gastroschisis differentiated from omphalocele in the newborn infant?

Both are ventral wall defects, yet their pathogenesis and prognosis differ markedly (Table 11.3).

Table 11.3 Differences Between Gastroschisis and Omphalocele

	GASTROSCHISIS	OMPHALOCELE
Incidence	1 in 10,000 (now increasing)	1 in 5000
Defect location	Right paraumbilical	Central
Covering sac	Absent	Present (unless sac ruptured)
Description	Free intestinal loops	Firm mass including bowel, liver, etc.
Associated with prematurity	50%-60%	10%-20%
Necrotizing enterocolitis	Common (18%)	Uncommon
Common associated anomalies	Gastrointestinal (10%-25%) Intestinal atresia Malrotation Cryptorchidism (31%)	Trisomy syndromes (30%) Cardiac defects (20%) Beckwith-Wiedemann syndrome Bladder exstrophy
Prognosis	Excellent for small defect	Varies with associated anomalies
Mortality	5%-10%	Varies with associated anomalies (80% with cardiac defect)

From Chabra S, Gleason CA. Gastroschisis: embryology, pathogenesis, epidemiology. *NeoReviews.* 2005;6:e493-e499.

32. Which conditions are associated with intra-abdominal calcifications?

Meconium peritonitis and **intra-abdominal tumors** are the most common disorders associated with intra-abdominal calcifications in the neonate. The calcifications of meconium peritonitis are streaky or plaquelike and occur over the abdominal surface of the diaphragm or along the flanks. Intra-intestinal calcifications appear as small, round densities that follow the course of the intestine and occur in association with intestinal stenoses, atresias, and aganglionosis. Intra-abdominal calcifications have also been observed in infants with adrenal hemorrhages and congenital infections.

33. What is NEC?

NEC is a necrotizing, inflammatory intestinal disorder that is the most common acquired gastrointestinal emergency in newborns. Signs and symptoms include abdominal distention and/or abdominal wall erythema, large or bilious gastric residuals or emesis, bloody stool, cardiorespiratory instability, and lethargy. A positive blood culture is found in 10% to 25% of cases at the time of diagnosis. Radiologic signs of NEC include dilated bowel loops, pneumatosis intestinalis, portal venous gas, and free intraperitoneal air if an intestinal perforation has occurred.

34. Is pneumatosis intestinalis pathognomonic for NEC?

No. Pneumatosis intestinalis can be seen in various other conditions, including Hirschsprung disease, pseudomembranous enterocolitis, neonatal ulcerative colitis, and ischemic bowel disease. However, it is a characteristic finding in the majority of patients with NEC. Dark, concentric rings within the bowel wall represent hydrogen as a by-product of bacterial metabolism (Fig. 11.4).

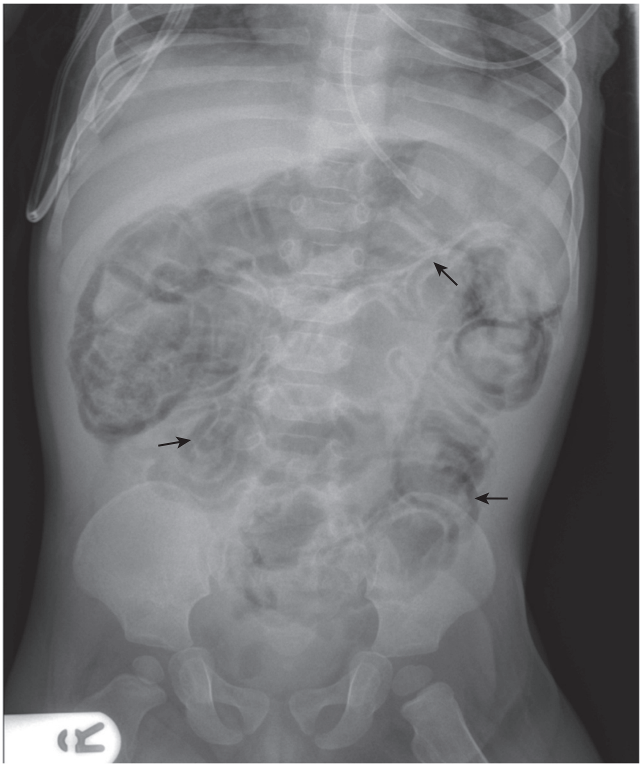

Fig. 11.4 Pneumatosis intestinalis with intramural gas *(arrows)*. (From George S, Cook J. Pneumatosis intestinalis. *J Pediatr.* 2014;16 (3):637.)

35. What are the most important risk factors for NEC in preterm infants?

The single greatest risk factor for NEC is **prematurity**, with the highest incidence (13%) occurring in infants <1000 g. Other variables associated with an increased risk for NEC include the use of a **ventilator on the first day of life**, **exposure to both glucocorticoids *and* indomethacin** during the first week of life (a cause of spontaneous

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intestinal perforation that may not be NEC), and **symptomatic patent ductus arteriosus** requiring surgery. A lower Apgar score is not related. The impact of race, gender, and antenatal steroids has varied between studies. Cesarean delivery and the use of breast milk were associated with a *lower risk* for surgical NEC.

Niño DF, Sodhi CP, Hackam DJ. Necrotizing enterocolitis: new insights into pathogenesis and mechanisms. *Nat Rev Gastroentero Hepatol.* 2016;13(10):590–600.

Fitzgibbons SC, Ching Y, Yu D, et al. Mortality of necrotizing enterocolitis expressed by birth weight categories. *J Pediatr Surg.* 2009;44(6):1072–1076.

Srinivasan PS, Brandler MD, D'Souza A. Necrotizing enterocolitis. *Clin Perinatol.* 2008;35(1):251–272.

36. Is there a role for probiotics in the prevention of NEC?

Probiotics are nonpathogenic bacteria that promote health when allowed to multiply within the gastrointestinal tract. In human breast milk, they consist primarily of *Lactobacillus* and *Bifidobacterium* species. Systematic reviews of multiple studies have revealed a reduction in the risk for NEC in infants >1000 g; infants <1000 g may not derive a benefit from probiotics. Furthermore, these trials had significant heterogeneity in the bacterial species, dose, and delivery. Additional studies are needed to demonstrate the safety and efficacy of probiotic products. Probiotics obtained from health food stores should not be used in preterm infants because of uncertainty about the composition.

Thomas JP, Raine T, Reddy S, Belteki G. Probiotics for the prevention of necrotising enterocolitis in very low-birth-weight infants: a meta-analysis and systematic review. *Acta Paediatr.* 2017;106(11):1729–1741.

AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev.* 2014; 4:CD005496.

Lewis ZT et al. Validating bifidobacterial species and subspecies identity in commercial probiotic products. *Pediatr Res.* 2016; 79(3):445–452.

HEMATOLOGIC ISSUES

37. When does the switch from fetal to adult hemoglobin synthesis occur in the neonate?

The switch from the production of hemoglobin F to hemoglobin A begins in a very programmed fashion in the fetus and neonate at **about 32 weeks of gestation**. At birth, about 50% to 65% of hemoglobin is type F.

38. Does the definition of anemia vary by gestational age?

For the term infant, most authorities consider a venous blood hemoglobin of <13 g/dL or a capillary hemoglobin of <14.5 g/dL consistent with anemia. In preterm infants >32 weeks of gestation, hematologic values differ only minimally from those of full-term infants, and therefore the same values may be used.

39. What changes in hemoglobin concentration are seen during the first few days of life?

In all newborn infants, hemoglobin levels rise slightly during the first few hours of life (because of hemoconcentration) and then fall somewhat during the remainder of the first day. In healthy full-term infants, the hemoglobin concentration then stays relatively constant for the rest of the first week of life. However, appropriate-for-gestational-age infants of <1500 g may show a decline of 1.0 to 1.5 g of hemoglobin per day during this same period.

40. When and at what dose should iron supplementation be initiated, and for how long should it be maintained?

The timing for initiation of iron supplementation in preterm infants has been a subject of controversy for decades. Recommendations of the AAP, Canadian Pediatric Society, and European Society of Pediatric Gastroenterology and Nutrition suggest that doses of 2 to 4 mg/kg per day of iron be initiated at 4 to 8 weeks of age and maintained for 12 to 15 months.

Rao R, Georgieff MK. Iron therapy for preterm infants. *Clin Perinatol.* 2009;36(1):27–42.

41. Should erythropoietin be used in preterm infants?

Despite many earlier studies demonstrating reticulocytosis and increased hematocrit after treatment with erythropoietin, the modest effect of treatment on the number of transfusions and volume transfused in milliliters has raised questions regarding its efficacy. Because the smallest, most immature infants are frequently transfused before the onset of the effects of erythropoietin, the patients may not experience any decrease in the number of donors to which they are exposed. Furthermore, studies have raised the question of whether the promotion of neovascularization by erythropoietin could result in an increased incidence of retinopathy of prematurity (ROP). Therefore at the present time, there is not enthusiasm for the use of this hormone to decrease transfusion requirements. Erythropoietin and similar erythropoiesis-stimulating agents are also being investigated as an adjunct therapy to prevent brain injury and to improve longer-term cognitive developmental outcomes.

Fischer HS, Reibel NJ, Bührer C, Dame C. Prophylactic early erythropoietin for neuroprotection in preterm infants: a meta-analysis. *Pediatrics.* 2017;139(5):e20164317.

Ohlsson A, Aher SM. Early erythropoiesis-stimulating agents in preterm or low birth weight infants. *Cochrane Database Syst Rev.* 2017;11:CD004863.

42. How can Rh disease be prevented?

Pregnant women who are Rh negative should have antibody screening at the time of initial presentation and a repeat antibody screen at about 28 weeks of gestation. Unsensitized Rh-negative women should receive 300 mg of Rh immunoglobulin (RhoGAM) prophylactically at 28 weeks' gestation and whenever an invasive procedure is performed. After delivery, if the infant is Rh positive, the mother should receive an additional dose of RhoGAM within 72 hours of delivery. At the time of delivery, the dose of RhoGAM may be increased if the fetomaternal hemorrhage is excessively large.

43. Why is the direct Coombs test frequently negative or weakly positive in infants with ABO incompatibility?

There are fewer A or B antigenic sites on the newborn red blood cells (RBCs), and there is a greater distance between antigenic sites compared with adult RBCs. In addition, there is absorption of serum antibody by ABO antigens located on tissues throughout the body.

44. If fetomaternal hemorrhage is suspected as a cause of neonatal anemia, how is this diagnosed?

The Kleihauer-Betke test, which detects the presence of fetal cells in the maternal circulation. Because fetal hemoglobin is resistant to elution with acid, the treatment of a maternal blood smear with acid will result in darkly stained fetal cells among the maternal "ghost" cells. From the percentage of fetal RBCs and the estimated maternal blood volume, the size of the hemorrhage can be determined. One percent of fetal cells in the maternal circulation indicates a bleed of about 50 mL.

45. If a gastric aspirate contains blood shortly after birth, what test can determine whether the blood is swallowed maternal blood or fetal hemorrhage?

Apt test. This test relies on the increased sensitivity of adult hemoglobin to alkali compared with fetal hemoglobin.

- *Method:* Mix the specimen with an equal quantity of tap water. Centrifuge or filter the specimen. The supernatant must have a pink color to proceed. To five parts of supernatant, add one part of 0.25 N (1%) NaOH.
- *Interpretation:* A pink color persisting for more than 2 minutes indicates fetal hemoglobin. Adult hemoglobin gives a pink color that becomes yellow in 2 minutes or less, thereby indicating the denaturation of hemoglobin.

46. How is polycythemia defined?

Polycythemia is defined by a peripheral venous hematocrit of 65% or hemoglobin >22 g/dL because these exceed the mean values found in normal newborns by two standard deviations. As the central venous hematocrit rises above 65%, there is an increase in viscosity. In neonates, some of the increase in viscosity with polycythemia is ameliorated by the lower viscosity of plasma. Because direct measurements of blood viscosity are not readily available in most laboratories, a high hematocrit level is thought to be the best indirect indicator of hyperviscosity.

47. What are the clinical manifestations of polycythemia?

In *symptomatic* infants, the most common presentations relate to CNS abnormalities, including lethargy, hypotonia, tremulousness, and irritability. Some infants will exhibit seizures. Hypoglycemia is commonly observed. Other organ systems can be involved, including the gastrointestinal tract (vomiting, distension, NEC), the kidneys (renal vein thrombosis, acute renal failure), and the cardiopulmonary system (respiratory distress, congestive heart failure, and persistent pulmonary hypertension of the newborn [PPHN]). However, infants with polycythemia are often *asymptomatic*.

48. Which infants with polycythemia should be treated?

There is controversy regarding guidelines for the need and types of treatment for polycythemia, with significant variability among academic centers. For *asymptomatic* newborns with peripheral venous hematocrits between 65 and 70, observation alone is one option, with careful attention to hydration, glucose, and bilirubin levels. Some centers will perform partial exchange transfusion (PET) for hematocrits $>70\%$ or $>75\%$ in *asymptomatic* infants. However, the benefits of PET for polycythemic newborns who are clinically well remain unproven. For *symptomatic infants,* some centers will provide IV hydration for hematocrits $>65\%$ and reserve PET for infants with severe symptoms (e.g., persistent hypoglycemia or unremitting cyanosis). Other clinicians are more aggressive and use PET for symptomatic infants with hematocrits $>65\%$. PET through an umbilical vein is associated with an increased risk for intestinal perforation.

Watchko JF. Common hematologic problems in the newborn nursery. *Pediatr Clin North Am.* 2015;62(2):509–524.

Hopewell B, Steiner LA, Ehrenkranz RA, et al. Partial exchange transfusion for polycythemia hyperviscosity syndrome. *Am J Perinatol.* 2011;28(7):557–564.

Morag I, Strauss T, Lubin D, et al. Restrictive management of neonatal polycythemia. *Am J Perinatol.* 2011;28(9):677–682.

Ozek E, Soll R, Schimmel MS. Partial exchange transfusion to prevent neurodevelopmental disability in infants with polycythemia. *Cochrane Database Syst Rev.* 2010;1:CD005089.

49. What is the definition of thrombocytopenia in the neonate?

Based on numerous studies, a normal platelet count in neonates of any viable gestational age is defined as $>150{,}000/\text{mm}^3$. However, counts in the 100,000 to 150,000/mm^3 range are frequently seen in healthy newborns. Consequently, patients with counts in this latter category should have repeat counts as well as further studies if illness is suspected.

Cremer M, Sallmon H, Kling PJ, et al. Thrombocytopenia and platelet transfusion in the neonate. *Semin Fetal Neonatal Med.* 2016; 21(1):10–18.

50. At what platelet count should platelet transfusion be considered?

Surveys of neonatologists reveal tremendous variability in the thresholds used for transfusion of platelets, especially because most are given prophylactically and not given to treat active bleeding. A 2019 study compared platelet transfusion at a threshold of 25,000/mm^3 to a threshold of 50,000/mm^3 in preterm infants born $<$34 weeks' gestation without a recent episode of major bleeding. In this study, infants treated with a platelet transfusion at the threshold of 50,000/mm^3 had a higher incidence of death or major bleeding within 28 days. This suggests that a lower platelet transfusion threshold may be better.

Curley A, Stanworth SJ, Willoughby K, et al. Randomized trial of platelet-transfusion thresholds in neonates. *N Engl J Med.* 2019; 380(3):242–251.

51. What features on physical examination suggest a specific cause of thrombocytopenia?

- "**Blueberry-muffin rash"**: **to**xoplasmosis **r**ubella **c**ytomegalovirus **h**erpes [TORCH] or viral infection
- **Absence of radii**: **t**hrombocytopenia **a**bsent **r**adii [TAR] syndrome
- **Palpable flank mass and hematuria**: renal vein thrombosis
- **Hemangioma, large,** often with bruit: Kasabach-Merritt syndrome
- **Abnormal thumbs**: Fanconi syndrome, although thrombocytopenia is less likely in newborns
- **Markedly dysmorphic features:** chromosomal abnormalities, particularly trisomy 13 or trisomy 18

52. What is the most common cause of severe thrombocytopenia in the first day of life?

Neonatal alloimmune thrombocytopenia (NAIT) occurs in 1 per 1000 newborn infants and is the most common cause of isolated severe thrombocytopenia in the first week of life. NAIT is due to a maternal alloantibody response to paternally inherited human platelet antigens (HPA), on fetal platelets. NAIT can occur with the first pregnancy, and it can result in thrombocytopenia severe enough to cause fetal intracranial hemorrhage. Identification of anti-HPA antibodies and HPA antigen typing of neonatal platelets will confirm the diagnosis. Some experts recommend treating otherwise-well infants with a platelet transfusion if the platelet count is $<$30,000/mm^3 or at higher thresholds if there is active bleeding or the infant is critically ill. Transfusion with random platelets may not be effective because the HPA antigens will be present on the transfused platelets, but is acceptable in an emergency. However, it is often possible to administer a specific HPA type to avoid continued destruction of the transfused platelets. In cases of persistent thrombocytopenia, intravenous immunoglobulin (IVIG) can be administered to the newborn infant.

Lieberman L, Greinacher A, Murphy MF, et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. *Br J Haematol.* 2019;185(3):549–562.

Winkelhorst D, Oepkes D, Lopriore E. Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies. *Expert Rev Hematol.* 2017;10(8):729–737.

53. What treatment is available during subsequent pregnancies for mothers who have had a child affected with NAIT?

NAIT recurs and increases in severity in subsequent pregnancies. With each subsequent pregnancy, the risk for the fetus should be assessed with platelet typing of the fetus using cell-free DNA in the maternal plasma. The mother can be treated with weekly infusions of IVIG as early as 12 weeks' gestation to minimize the incidence of thrombocytopenia and intracranial hemorrhage. Some experts recommend maternal treatment with corticosteroids (prednisone) in addition to IVIG later in gestation.

Lieberman L, Greinacher A, Murphy MF, et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. *Br J Haematol.* 2019;185(3):549–562.

54. When do the prothrombin time and partial thromboplastin time "normalize" to adult values?

The *prothrombin time* reaches adult values at **about 1 week of age**, whereas the *partial thromboplastin time* does not attain adult values until **2 to 9 months of age**.

55. How is disseminated intravascular coagulation (DIC) diagnosed in the neonate?

The laboratory findings of *DIC* include evidence of RBC fragmentation on peripheral smear; elevation of prothrombin time, partial thromboplastin time, and thrombin time; thrombocytopenia; decreased levels of factors V, VIII, and fibrinogen; and in some cases, the presence of fibrin split products.

56. How should newborn infants with DIC be managed?

Treatment should be directed primarily at the underlying disease rather than at the coagulation defects. In most instances, treatment of the former makes specific treatment of the latter unnecessary. However, when stabilization of coagulopathy is not imminent, replacement of coagulation factors with fresh frozen plasma and platelets is recommended. In cases in which fluid overload is a major concern, exchange transfusion with fresh whole blood may be used. However, this second approach is not superior to the first with respect to the resolution of DIC. The use of heparin in patients with DIC is currently reserved for cases of thrombosis of major vessels or purpura fulminans.

57. What are the different ways that vitamin K deficiency bleeding (VKDB) may manifest?

This condition was formerly called *hemorrhagic disease of the newborn.* For evolutionary reasons that are unclear, a newborn has only about 50% of the normal vitamin K–dependent cofactors, which play major roles in coagulation pathways. Unless vitamin K is given intramuscularly as part of recommended newborn prophylaxis, these levels steadily decline during the first 3 days of life. In addition, breast milk is low in vitamin K. Early hemorrhagic disease can be observed during the first few days of life in infants who are exclusively breastfed and who do not receive vitamin K prophylaxis at birth (classic VKDB). These infants may bleed from various sites (e.g., umbilical cord, circumcision). Infants born to mothers who have received medications that affect the metabolism of vitamin K (e.g., warfarin, antiepileptic medications, antituberculous drugs) are at risk for developing severe life-threatening intracranial hemorrhages in an earlier time frame, either at or shortly after delivery (early-onset VKDB). VKDB can occur with late-onset disease between 3 weeks and 8 months of age and may also present with catastrophic neurologic complications, including intracranial hemorrhage and seizures.

Sankar MJ, Chandrasekaran A, Kumar P, et al. Vitamin K prophylaxis for prevention of vitamin K deficiency bleeding: a systematic review. *J Perinatol.* 2016;36(Suppl 1):S29–35.

58. Why are premature infants at increased risk for the need for transfusions?

Transfusion needs are greater in premature infants due to lower erythropoietin production, phlebotomy blood loss, and reduced RBC life span. Up to 90% of very low-birth-weight infants and up to 60% of preterm infants $<$32 weeks may require RBC transfusions.

Howarth C, Banerjee J, Aladangady N. Red blood cell transfusion in preterm infants: current evidence and controversies. *Neonatology.* 2018;114(1):7–16.

59. What are the risks and benefits of restrictive versus liberal transfusion criteria in preterm infants?

The optimal hematocrit threshold below which a premature infant should be transfused remains uncertain. Anemia may cause apnea and bradycardia and result in poorer neurodevelopmental outcomes and suboptimal weight gain. However, transfusions may be associated with infections, NEC (cause and effect unproven), and circulatory overload. A key question is whether a more “restrictive” (i.e., lower) or “liberal” (i.e., higher) hemoglobin level results in a better balance of risks and benefits.

Two studies (Iowa and PINT) assigned preterm infants to liberal (10.0 to 15.3, Iowa trial; 8.5 to 13.5, PINT trial) compared with similar restrictive (7.3 to 11.3, Iowa trial; 7.5 to 11.5, PINT trial) hemoglobin thresholds depending on postnatal age and respiratory support. The Iowa trial demonstrated a reduction in the number of transfusions, and the PINT trial had fewer donor exposures in the restrictive group. However, the liberal transfusion group in the Iowa trial (which had higher hemoglobin levels) demonstrated a reduction in brain injury and the combined outcome of brain injury or death. This questions whether a policy severely limiting transfusions is beneficial for tiny premature infants. The ongoing TOP (Transfusion of Prematures) Trial, a National Institute of Child Health and Human Development study designed to assess the best transfusion strategy to improve neurologically intact survival of extremely premature infants, may provide an answer.

Howarth C, Banerjee J, Aladangady N. Red blood cell transfusion in preterm infants: current evidence and controversies. *Neonatology.* 2018;114(1):7–16.
Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized controlled trial of a restrictive vs. liberal transfusion threshold for extremely low birth weight infants. *J Pediatr.* 2006;149(3):301–307.
Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal vs. restrictive guidelines for red blood cell transfusions in preterm infants. *Pediatrics.* 2005;115(6):1685–1691.

HYPERBILIRUBINEMIA

60. What are the normal changes in bilirubin levels in full-term healthy newborns?

All newborn infants exhibit a progressive rise in serum bilirubin concentrations after birth. Beginning with an average bilirubin in cord blood of 2 mg/dL, serum levels rise and peak between 48 and 120 hours of life. The 97th percentile for bilirubin in healthy full-term infants is 12.4 mg/dL for bottle-fed infants and 14.8 mg/dL for breastfed infants. If untreated, at least 1% to 2% of newborns will develop bilirubin levels of 20 mg/dL.

61. What neonatal risk factors are associated with hyperbilirubinemia?

- ABO incompatibility
- Lower gestational age
- Exclusive breastfeeding, particularly if nursing $<$8 times per day or if excessive weight loss
- Jaundice in first 24 hours
- Isoimmune or other hemolytic disease (e.g., G6PD deficiency)

- Previous sibling with jaundice
- Cephalohematoma or significant bruising
- East Asian race

Pace EJ, Brown CM, DeGeorge KC. Neonatal hyperbilirubinemia: an evidence-based approach. *J Fam Pract.* 2019;68(1):E4–E11.
AAP Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114(1):297–316.

62. What screening tests should pregnant women have to identify infants at risk for hyperbilirubinemia?

All pregnant women should be tested for ABO and Rh(D) blood types and have a serum screen for unusual isoimmune antibodies.

AAP Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114(1):297–316.

63. Which infants are "set-ups" for ABO incompatibility?

Infants who are type A or B and whose mothers are type O. In mothers with type A or B blood, naturally occurring anti-A and anti-B isoantibodies are primarily IgM and do not cross the placenta. However, in mothers with type O blood, isoantibodies are frequently IgG. These antibodies can cross the placenta and cause hemolysis. Although about 12% of maternal–infant pairs qualify as "set-ups" for ABO incompatibility, <1% of infants have significant hemolysis.

64. What distinguishes breastfeeding jaundice from breast milk jaundice?

Hyperbilirubinemia in breastfed infants during the first week of life is called *breastfeeding jaundice* and is thought to be the result of poor caloric intake and/or mild dehydration. Hyperbilirubinemia in breastfed infants after the first week of life is known as *breast milk jaundice*. The cause of breast milk jaundice is uncertain; however, possible etiologies include an increased enterohepatic circulation of bilirubin as a result of the presence of β-glucuronidase in human milk and/or the inhibition of the hepatic glucuronosyl transferase by a factor such as free fatty acids in some human milk samples. The incidence and duration compared with physiologic jaundice are noted in Table 11.4.

Table 11.4 Comparison of Physiologic, Breastfeeding, and Breast Milk Jaundice

	PHYSIOLOGIC JAUNDICE	BREASTFEEDING JAUNDICE	BREAST MILK JAUNDICE
Time of onset (TSB >7 mg/dL)	After 36 hr	2-4 days	4-7 days
Usual time of peak bilirubin	3-4 days	3-6 days	5-15 days
Peak TSB	5-12 mg/dL	>12 mg/dL	>10 mg/dL
Age when total bilirubin <3 mg/dL	1-2 wk	>3 wk	9 wk
Incidence in full-term neonates	56%	12%-13%	2%-4%

TSB, Total serum bilirubin.
From Gourley G. Pathophysiology of breast milk jaundice. In Polin RA, Fox W, eds. *Fetal and Neonatal Physiology.* Philadelphia, PA: W.B. Saunders; 1992:1174.

65. Why should infants at risk for breastfeeding jaundice be fed more frequently?

Breastfed infants exhibit their maximal weight loss by day 3 of life and lose on average 6.1% ± 2.5% of their birth weight. Infants breastfed an average of more than eight times per day during the first 3 days of life have significantly lower serum bilirubin concentrations than those who are breastfed less frequently. This practice accelerates and enhances the acquisition of milk supply. With increased milk available, dehydration is less likely to occur, and the excretion of bilirubin by the gastrointestinal tract is more rapid. Infants with adequate intake should have four to six wet diapers per day.

66. How should infants be assessed for jaundice (hyperbilirubinemia) before discharge?

The AAP recommends evaluation of hyperbilirubinemia with predischarge total serum bilirubin (or transcutaneous bilirubin) in combination with an assessment of clinical risk factors. Predischarge bilirubins should be plotted on the chart in Fig. 11.5 to assess the risk that the infant will ultimately need therapy for hyperbilirubinemia. This risk level can be used to plan follow-up timing.

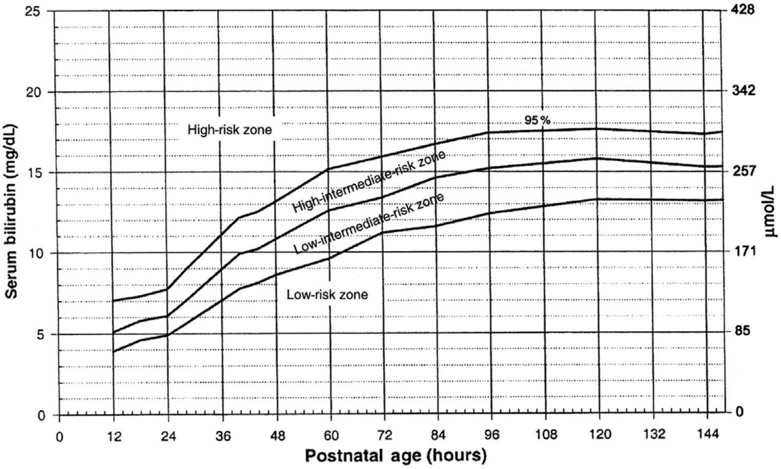

Fig. 11.5 Assessment of jaundice. (From Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297–316.)

67. What is the fraction of bilirubin that is believed to be toxic to the CNS?

Routine clinical laboratory tests measure the total bilirubin and the conjugated bilirubin. Of the total unconjugated bilirubin, most is bound to albumin and thus cannot cross the blood–brain barrier. Although **free bilirubin** is believed to cause neurotoxicity, routine measurement in clinical practice is not available. Therefore clinical decisions are commonly based on the total bilirubin concentration. It is unclear if monitoring the bilirubin/albumin ratio is of value.

Watchko JF, Tiribeli C. Bilirubin-induced neurologic damage—mechanisms and management approaches. *N Engl J Med.* 2013; 369(21):2021–2030.

Ahlfors CE. Predicting bilirubin neurotoxicity in jaundiced infants. *Curr Opin Pediatr.* 2010;22(2):129–133.

68. What are the clinical features of bilirubin toxicity?

The early clinical manifestations of bilirubin toxicity can be subtle. In addition, they can progress rapidly to severe and life-threatening manifestations. Acutely, toxicity is called *bilirubin-induced neurologic dysfunction* (BIND). For chronic cases, the term *kernicterus* is generally used. Using the BIND score, infants with subtle signs of bilirubin toxicity can be identified (Table 11.5).

Table 11.5 Clinical Features of Bilirubin-Induced Neurologic Dysfunction (BIND)

SIGNS	MILD	MODERATE	SEVERE
Behavior	Too sleepy Decreased feeding Decreased vigor	Lethargy and/or irritability (depending on arousal state) Very poor feeding	Semicoma Apnea Extreme irritability Seizures Fever
Muscle tone	Slight but persistent decrease in tone	Mild to moderate hypertonicity Mild nuchal or truncal arching	Severe hypotonia or hypertonia Atonic Opisthotonic posturing, bicycling
Cry pattern	High-pitched	Shrill and piercing (especially when stimulated)	Inconsolable, very weak, and cries only with stimulation

69. When should phototherapy be instituted in infants who are at least 35 weeks of gestational age?

AAP guidelines for instituting phototherapy in term and near-term infants are shown in Fig. 11.6.

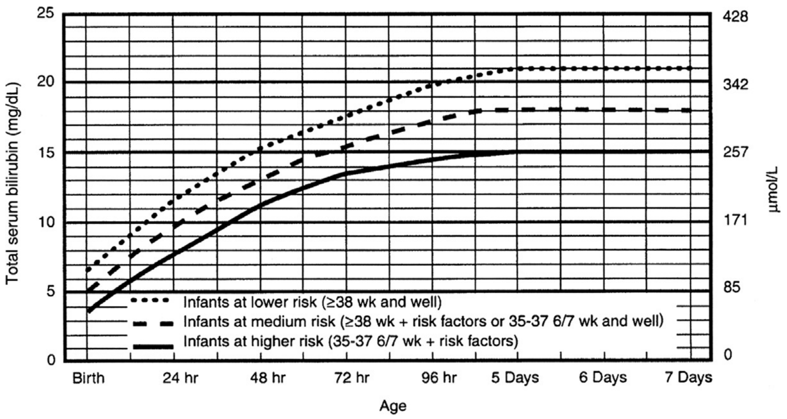

Fig. 11.6 American Academy of Pediatrics guidelines for instituting phototherapy. (From Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316.)

70. Where does bilirubin go when you turn on the lights?

It becomes **lumirubin** (through a "cyclicization" reaction) and is rapidly excreted in bile, with a half-life of about 2 hours.

71. What are the factors that affect the efficacy of phototherapy?

- **Spectrum of light emitted** (blue-green is most effective)
- **Spectral irradiance** (intensive phototherapy $=$ 30 W/cm^2 per nm)
- **Spectral power** (expose maximal surface area)
- **Cause of jaundice** (phototherapy is less effective with hemolysis and cholestasis)
- **Total bilirubin at start** (the higher the bilirubin, the greater the decline)

Bhutani VK, Committee on Fetus and Newborn. Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2011;128(4):e1046–e1052.
AAP Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114(1):297–316.

72. What are the contraindications to phototherapy?

Infants with a family history of **light-sensitive porphyria** should not receive phototherapy. Of note, the presence of direct hyperbilirubinemia is not considered a contraindication, but it will decrease the effectiveness of phototherapy and may result in bronze baby syndrome.

73. What are the common adverse effects of phototherapy?

Loose stools, increased insensible **water loss**, **skin rashes**, **overheating**, and the potential for **burns** if the heat-emitting lights are placed too close to the infant's skin. If direct hyperbilirubinemia is present, **bronze baby syndrome** can result.

Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. *N Engl J Med.* 2008;358(9):920–928.

74. A newborn develops dark skin discoloration and dark urine after beginning phototherapy. What is the diagnosis?

Bronze baby syndrome. Infants who develop the syndrome typically have an elevated direct serum bilirubin concentration. The bronze baby syndrome results from the retention of photoproducts (e.g., lumirubin) that cannot be excreted in the bile. Most infants appear to recover without complications. Direct hyperbilirubinemia is not a contraindication to phototherapy.

75. What are the complications of exchange transfusions in the newborn?

Acute

- Hypocalcemia (as a result of the binding of calcium by citrate)
- Hypoglycemia
- Intestinal perforation
- Thrombocytopenia (as a result of the removal of platelets and the use of stored blood that may be low in platelets)
- Hyperkalemia (as a result of the higher potassium levels of stored blood)

- Hypovolemia (if blood replacement is inadequate)
- Diminished oxygen delivery (if blood stored for >5 to 7 days is used, the resultant loss of 2,3-diphophoglycerate may have deleterious effects on oxygen delivery)

Late

- Anemia (for unknown reasons)
- Graft-versus-host disease (as a result of the introduction of donor lymphocytes into a relatively immunocompromised neonatal host)

76. What is the relationship between delayed neonatal jaundice and urinary tract infection (UTI)?

Unexplained jaundice developing between 10 and 60 days of age can be associated with a UTI in infants. The typical patient is usually afebrile with hepatomegaly and minimal systemic symptoms. Hyperbilirubinemia is usually conjugated, and liver transaminases may be normal or mildly elevated. Treatment of the UTI (usually caused by *Escherichia coli*) results in reversal of the liver dysfunction, which is believed to be the result of endotoxins.

77. Can transcutaneous bilirubin measurements be used in place of serum levels?

Numerous devices have been developed that accurately measure bilirubin levels. However, most studies show that the deviation of transcutaneous measurements is greatest (about 3 mg/dL) at the highest levels (>13 to 15 mg/dL). Therefore many authorities recommend serum confirmation if the transcutaneous bilirubin is greater than the 75th percentile, more than 13 mg/dL, or if a level that is 3 mg/dL higher would be clinically meaningful.

Hassan Shabuj M, Hossain J, Dey S. Accuracy of transcutaneous bilirubinometry in the preterm infants: a comprehensive meta-analysis. *J Matern Fetal Neonatal Med.* 2019;32(5):734–741.

O'Connor MC, Lease MA, Whalen BL. How to use: transcutaneous bilirubinometry. *Arch Dis Child Educ Pract Ed.* 98(4):154–159.

78. What is the role of IVIG use in the treatment of hyperbilirubinemia?

Several studies in the 1990s suggested that high-dose IVIG was effective in decreasing the need for exchange transfusion in infants who were Coombs positive. However, these studies had design flaws, and subsequent studies have not confirmed these results. The efficacy of IVIG in the setting of Rh hemolytic disease of the newborn remains uncertain.

Zwiers C, Scheffer-Rath ME, Lopriore E, et al. Immunoglobulin for alloimmune hemolytic disease in neonates. *Cochrane Database Syst Rev.* 2018;3:CD003313.

79. Who is considered the discoverer of contemporary phototherapy for neonatal jaundice?

Sister Jean Ward. In the early 1950s, Sister Ward was the nurse in charge of the unit for premature infants at Rochford General Hospital in Essex, England. On warm summer days, Sister Ward would take her infants to the courtyard to give them fresh air and sunshine. It was following such an afternoon of sunshine that Sister Ward observed that sunlight was able to "bleach" the skin of jaundiced newborns. One particular infant was noted to have a demarcated triangle of skin (covered by the corner of a sheet while in the sunshine) that was much yellower than the rest of the body. These observations became the springboard at the same hospital for studies describing how bilirubin levels in icteric sera were lowered when exposed to sunlight and certain blue lights. The important lesson is: always listen to your nursing staff!

Maisels MJ. Sister Jean Ward, phototherapy and jaundice: a unique human and photochemical interaction. *J Perinatol.* 2015;35(9):671–675.

INFECTIOUS DISEASE ISSUES

80. What is the best method of umbilical cord care during the immediate neonatal period?

No single method of cord care has been determined to be superior for preventing colonization and infections. Antimicrobial agents, such as bacitracin or triple dye, are commonly used, but there are no efficacy data (other than reduced colonization). Alcohol accelerates the drying of the cord, but it has not been shown to reduce the rates of colonization or omphalitis. The use of topical antibiotics has been shown to delay cord separation. Therefore, simply cleaning with normal saline and allowing the cord to dry normally appears to be as safe and effective as using antibiotics.

Stewart D, Benitz W. Umbilical cord care in the newborn infant. *Pediatrics.* 2016;138(3):e20162149.

81. Can sepsis be distinguished from other causes of respiratory distress in the neonate?

Not reliably. Diagnosis is confirmed only by a positive blood, urine, or cerebrospinal fluid (CSF) culture.

82. What is the single most important factor in determining whether a newborn should be evaluated and treated for possible sepsis?

Clinical signs of sepsis. An infant with clinical signs of sepsis should be evaluated with appropriate cultures and treated with antibiotics. Risk factors for sepsis include maternal group B streptococcal (GBS) colonization, chorioamnionitis, prematurity, and rupture of membranes >18 hours. Determining whether to evaluate *asymptomatic infants* with risk factors for sepsis is more difficult. Guidelines for the management of these infants have changed over recent years and continue to evolve. The goal of management continues to be to identify infants with evolving sepsis who truly require antibiotic therapy before they become symptomatic and who could have significant morbidity and even mortality without treatment. However, it is also desirable to minimize treatment in infants who do not have infection. Unfortunately, there is no perfect method to identify only infants with true infection, and clinicians must use sound judgment and familiarize themselves with the most current guidelines.

Good PI, Hooven TA. Evaluating newborns at risk for early-onset sepsis. *Pediatr Clin North Am.* 2019;66(4):321–331.

Hooven TA, Randis TM, Polin RA. What's the harm? Risks and benefits of evolving rule-out sepsis practices. *J Perinatol.* 2018; 38(6):614–622.

Hooven TA, Polin RA. Time to overhaul the "rule-out sepsis" work-up. *Pediatrics.* 2017;140(1):e20171155.

83. Should a lumbar puncture (LP) be performed on all newborns as part of the sepsis evaluation?

The need for an LP as part of the sepsis evaluation of a newborn is controversial, with some authors suggesting its omission in *asymptomatic* infants. However, in *symptomatic* infants with a **high suspicion of sepsis**, an LP should be strongly considered. It is worth remembering that (1) bacterial meningitis can be present in newborns without CNS symptoms; (2) a significant number of infants (15% to 30%) can have meningitis without bacteremia, especially after the first week of life; and (3) meningitis can coexist in premature infants with suspected RDS. The procedure should be postponed in an infant with cardiorespiratory instability or significant thrombocytopenia.

Srinivasan L, Harris MC, Shah SS. Lumbar puncture in the neonate: challenges in decision making and interpretation. *Semin Perinatol.* 2012;36(6):445–453.

Stoll BJ, Hansen N, Fanaroff AA, et al. To tap or not to tap: high likelihood of meningitis without sepsis among VLBW infants. *Pediatrics.* 2004;113(5):1181–1186.

Wiswell TE, Baumgart S, Gannon CM, Spitzer AR. No lumbar puncture in the evaluation for early neonatal sepsis: will meningitis be missed? *Pediatrics.* 1995;95(6):803–806.

84. What are the contraindications to performing an LP?

- Uncorrected thrombocytopenia or bleeding diathesis
- Infections in the skin or underlying structures adjacent to the puncture site
- Lumbosacral anomalies
- Cardiorespiratory instability
- Increased intracranial pressure: Although the presence of open sutures reduces the likelihood of herniation, this remains a possibility. In the presence of a rapidly deteriorating level of consciousness, cranial nerve palsies, abnormal posturing, abnormalities of vital signs without other cause, and/or a tense fontanelle, brain imaging (computed tomography or magnetic resonance imaging [MRI]) should be obtained before performing an LP.

MacDonald MG, Ramasethu J. *Atlas of Procedures in Neonatology.* 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.

85. What are normal CSF values for healthy neonates?

- The mean number of white blood cells (WBC) in a healthy infant is 5. More than 15 WBCs in a CSF sample should be considered suspect, and >21 WBCs in a CSF sample should be considered elevated.
- Protein levels in CSF >100 mg/dL should be considered suspect in a term infant. However, protein concentrations are known to vary with gestational age and are often >100 mg/dL in preterm infants without meningitis.
- Glucose levels in CSF should be 70% to 80% of blood concentrations in term and preterm infants.

Garges HP, Moody MA, Cotton CM, et al. Neonatal meningitis: what is the correlation among CSF cultures, blood cultures and CSF parameters? *Pediatrics.* 2006;117(4):1094–1100.

Sarff, LD, Platt LH, McCracken GH Jr. Cerebrospinal fluid evaluation in neonates: comparison of high-risk infants with and without meningitis. *J Pediatr.* 1976;88(3):473–477.

86. What is the preferred strategy for identifying women for intrapartum GBS prophylaxis?

Universal screening is recommended. It is estimated that the prevalence of vaginal or rectal colonization with GBS is between 10% and 30% in pregnant women. The 2019 ACOG guidelines recommend that all pregnant women be screened with vaginal and rectal cultures at $36^{0/7}$ to $37^{6/7}$ weeks' gestation. Nucleic acid amplification tests (NAATs) may also be used, as results have been found to be equivalent to culture-based screening. The 2010 Centers for

Disease Control and Prevention (CDC) guidelines call for screening starting at $35^{0/7}$ weeks. Earlier guidelines from the CDC had recommended a risk-based approach monitoring women with obstetric factors (e.g., maternal fever, rupture of membranes >18 hours). Analysis revealed that the risk factor–based strategy identified <50% of affected infants' mothers compared with 85% to 90% with universal culture-based screening. Although the incidence of early-onset neonatal sepsis due to GBS has been reduced by 80% since the 1990s (when national guidelines for intrapartum antibiotic prophylaxis were first implemented), GBS remains the leading infectious cause of morbidity and mortality among infants in the United States.

ACOG Committee Opinion No. 782. Prevention of early-onset Group B streptococcal disease in newborns. *Obstet Gynecol.* 2019;134: e19–e40.

Verani JR, McGee L, Schrag S. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep.* 2010;59(RR-10):1–36.

87. Which women should receive intrapartum antibiotic prophylaxis?

According to the 2010 CDC and 2019 ACOG guidelines, antibiotic prophylaxis is recommended for women with a *positive* GBS screening test within 5 weeks of delivery, GBS bacteriuria any time during pregnancy, or a previous infant with invasive GBS disease. For women with *unknown* GBS status, intrapartum antibiotic prophylaxis should be given if there is prolonged rupture of membranes >18 hours or a temperature of ≥100.4°F. Furthermore, given that preterm delivery is a key risk factor for early-onset GBS disease, both the CDC and ACOG guidelines recommend screening for GBS and antibiotic prophylaxis pending testing results for all women with unknown GBS status and onset of labor <37 weeks' gestation. Intrapartum antibiotic prophylaxis is NOT recommended for routine, planned caesarean sections before the onset of labor with intact amniotic membranes.

ACOG Committee Opinion No. 782. Prevention of early-onset group B streptococcal disease in newborns. *Obstet Gynecol.* 2019;134: e19–e40.

Schrag SJ, Verani JR. Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: experience in the United States and implications for a potential group B streptococcal vaccine. *Vaccine.* 2013;31(Suppl 4):D20–26.

Verani JR, McGee L, Schrag S. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep.* 2010;59(RR-10):1–36.

88. What are the typical clinical presentations of early-onset GBS disease compared with late-onset disease?

Early-onset GBS sepsis typically presents in the first 24 to 48 hours of life with signs of **respiratory distress** and **hemodynamic instability**. Other signs of sepsis can include apnea, hypothermia, hypoglycemia, vomiting, and lethargy. Most commonly infants with early-onset GBS disease have sepsis or pneumonia, and less frequently they have meningitis. Meningitis, osteomyelitis, and septic arthritis are more common clinical presentations of *late-onset* disease, defined as GBS infections occurring 7 days to 3 months after birth.

Koenig, JM, Keenan, WJ. Group B streptococcus and early-onset sepsis in the era of maternal prophylaxis. *Pediatr Clin North Am.* 2009; 56(3):689–708.

89. Do intrapartum antibiotics change the clinical presentation of early-onset GBS sepsis?

No. Although intrapartum antibiotic use reduces the incidence of early-onset GBS sepsis, it does not completely eliminate early-onset GBS sepsis. Furthermore, the presentation of early-onset GBS sepsis is unchanged by the use of intrapartum antibiotic prophylaxis. In a study of 319 infants with early-onset GBS disease, the administration of intrapartum antibiotics to the mother did not affect the constellation and timing of clinical signs of disease. All infants born to pretreated mothers became ill during the first 24 hours of life (80% within the first 6 hours of life).

Bromberger P, Lawrence JM, Braun D, et al. The influence of intrapartum antibiotics on the clinical spectrum of early-onset group B streptococcal infection in term infants. *Pediatrics.* 2000;106(2 Pt 1):244–250.

90. What are the most common pathogens that are responsible for late-onset sepsis in the newborn infant?

- Coagulase-negative staphylococci (48%)
- Gram-negative enterics (18%)
- *Candida* species (10%)
- *Staphylococcus aureus* (8%)
- *Enterococcus* species (3%)

Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics.* 2002;110(2 Pt 1):285–291.

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Pediatrics & Neonatology Journals
[Ahmed Manfy] on TELEGRAM

91. What are the key strategies for the prevention of health care–associated infections in the neonatal intensive care unit (NICU)?

- **Hand hygiene**: meticulous hand hygiene remains the most effective way to reduce health care–associated infections in the NICU
- **Central line care**: attention to insertion and maintenance practices in combination with efforts to decrease duration of central lines
- Increased use of **human milk**
- Use of **standard** and specialized **isolation precautions**
- **Judicious use** of antibiotic therapy
- **Vaccination** of health care workers and families

Polin RA, Denson S, Brady MT. Strategies for prevention of health care-associated infections in the NICU. *Pediatrics.* 2012;129(4): e1085–e1093.

92. Is methicillin-resistant *S. aureus* (MRSA) a significant pathogen in the NICU?

A 2017 meta-analysis demonstrated that up to 6% of infants admitted to the NICU were colonized with MRSA. A further 6% of neonates acquired MRSA colonization during their NICU admission. These infants were at higher risk (RR $=$ 24) of developing invasive MRSA disease during hospitalization compared with uncolonized neonates. Infants with lower gestational age and lower birth weight were at highest risk for colonization. In NICUs with evidence of high rates of MRSA nasal colonization, treatment with nasal mupirocin is recommended by many authorities, but benefits are unproven.

Washam M, Woltmann J, Haberman B, et al. Risk factors for methicillin-resistant *Staphylococcus aureus* colonization in the neonatal intensive care unit: a systematic review and meta-analysis. *Am J Infect Control.* 2017;45(12):1388–1393.

Zervou FN, Zacharioudakis IM, Ziakas PD, Mylonakis E. MRSA colonization and risk of infection in the neonatal and pediatric ICU: a meta-analysis. *Pediatrics.* 2014;133(4):e1015–e1023.

93. How is systemic candidiasis diagnosed in the neonate?

Candidiasis is diagnosed by cultures of blood, urine, and CSF or other body fluids that are generally sterile. Because cultures are only intermittently positive, multiple systemic cultures should be obtained. A urinalysis demonstrating budding yeasts or hyphae should raise suspicion of systemic infection. Gram stains of buffy coat smears may also demonstrate organisms. An ophthalmologic examination may indicate the presence of candidal endophthalmitis. Renal and brain ultrasounds should be performed to look for characteristic lesions. In addition, echocardiography should be performed in infants with central catheters to rule out cardiac vegetations.

94. Should preterm infants receive prophylaxis for the prevention of *Candida* infections?

A number of studies have examined the role of fluconazole prophylaxis in reducing mortality, infections, and colonization among infants with very low birth weight. Although reduced mortality was not a consistent finding, decreased colonization and invasive infections were consistently seen. A large trial of infants $<$750 g (the highest-risk group) found no long-term benefit to prophylactic fluconazole. Concerns remain that use of this high-cost treatment will increase fluconazole resistance and the emergence of *Candida glabrata* and *Candida krusei,* which are inherently less sensitive to the drug.

Autmizguine J, Smith PB, Prather K, et al. Effect of fluconazole prophylaxis susceptibility in premature infants. *J Antimicrob Chemother.* 2018;73(12):3482–3487.

Benjamin DK, Hudak ML, Duara S, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. *JAMA.* 2014;311(17):1742–1749.

Carey AJ, Saiman L, Polin RA. Hospital-acquired infections in the NICU: epidemiology for the new millennium. *Clin Perinatol.* 2008; 35(1):223–249.

95. What is the risk for prenatal viral transmission in infants born to mothers with hepatitis B or hepatitis C?

- *Hepatitis B*: If a mother is HBsAg and HBeAg positive, the risk for transmission is 70% to 90%. The risk is substantially lowered to 5% to 20% if the mother is HBsAg positive but HBeAg negative. Infants infected in the perinatal period have a greater than 90% chance of developing chronic hepatitis B infection, and of these, 25% go on to develop hepatocellular carcinoma.
- *Hepatitis C*: If a mother has chronic hepatitis C virus (HCV) infection (defined as HCV antibody and RNA positive), transmission rate to an infant at 18 months is 4% to 8% for women with HCV infection alone and 8% to 15% for women with both HCV and HIV infection. Risk varies depending on the concentration of maternal HCV RNA at the time of birth. Of note, maternal antibodies persist until at least 18 months, so serologic testing of an infant for HCV antibodies should not be done before 18 months of age.

Post JJ. Update on hepatitis C and implications for pregnancy. *Obstet Med.* 2017;10(4):157–160.

Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology.* 2001;34(2):223–229.

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96. Should preterm infants receive hepatitis B vaccine during their newborn stay in the hospital?

Given the efficacy of the hepatitis B vaccine, the AAP now recommends administration of hepatitis B vaccine within 24 hours to all infants >2000 g. Given the possibility of immature response to vaccine at birth, in infants with birth weight <2000 g, hepatitis B vaccination should be delayed until 1 month of age or hospital discharge, whichever comes first. If the infant's mother is HbsAg positive or status unknown, vaccine must be administered along with hepatitis B immunoglobulin (HBIG) within 12 hours of birth, regardless of birth weight.

Committee on Infectious Diseases, Committee on Fetus and Newborn. Elimination of perinatal hepatitis B: providing the first vaccine dose within 24 hours of birth. *Pediatrics.* 2017;140(3):e20171870.

97. What prophylactic medications should be given to infants ≥35 weeks born to HIV-positive mothers?

Women with HIV infection should be treated with antiretroviral therapy during pregnancy with a goal of achieving a minimal viral load. For women who were treated during pregnancy and had adequate viral suppression, the newborn infants may be treated with zidovudine for 4 to 6 weeks. For women who were untreated during pregnancy or only received intrapartum prophylaxis, the newborn infants should be treated with zidovudine for 6 weeks and nevirapine for three doses during the first week of life, according to current recommendations. Treatment should begin as soon as possible after birth.

American Academy of Pediatrics. Human immunodeficiency virus infection. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:474.

METABOLIC ISSUES

98. In what settings should inborn errors of metabolism be suspected?

Symptoms related to diet

- Onset of symptoms that correlates with dietary changes
- Patient with strong food preferences or aversions
- Unexplained failure to thrive, vomiting, or poor feeding

Symptoms related to family history

- Parental consanguinity
- Unexplained sibling death, mental retardation, or seizures

Physical examination findings

- Unusual odor
- Hair abnormalities, especially alopecia
- Microcephaly or macrocephaly
- Abnormalities of muscle tone
- Organomegaly
- Coarsened facial features, thick skin, limited joint mobility, and hirsutism

Developmental changes

- Loss or leveling of developmental milestones
- Lethargy

Levy PA. Inborn errors of metabolism. *Pediatr Rev.* 2009;30(4):131–138.

99. One of the key presenting features of inborn errors of metabolism is the presence or absence of metabolic acidosis. Which inborn errors of metabolism present with metabolic acidosis?

- Presenting with metabolic acidosis *with* lactic acidemia
  - Defects in gluconeogenesis, glycogenolysis, or pyruvate metabolism (e.g., glycogen storage disease, fructose-1,6-diphosphatase deficiency, pyruvate carboxylase, or dehydrogenase deficiency)
  - Krebs cycle defects
  - Respiratory chain defects
- Presenting with metabolic acidosis *without* lactic acidemia
  - Maple syrup urine disease
- Presenting with metabolic acidosis and *variable* presence of lactic acidemia
  - Organic acidemias (e.g., propionic acidemia, methylmalonic acidemia, isovaleric acidemia)
  - Fatty acid oxidation defects

Martin RJ, Fanaroff AA, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant.* 9th ed. St. Louis, MO: Elsevier; 2011;1659–1675.

100. When is hypoglycemia most likely to occur in a neonate?

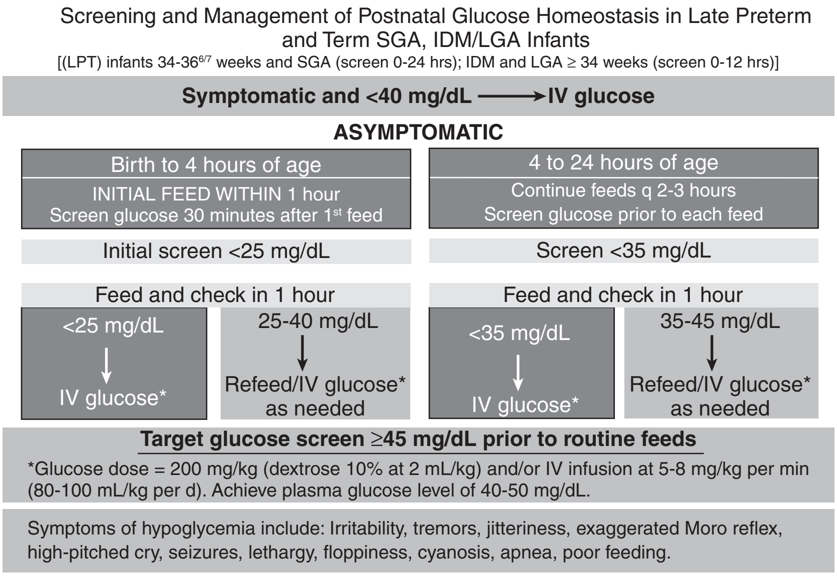
During gestation, glucose is freely transferred across the placenta by the process of facilitated diffusion. However, after birth, the infant must adjust to the sudden withdrawal of this transplacental supply. In all infants, there is a nadir in blood sugar between 1 and 3 hours of life. During the first 12 to 24 hours of life, newborns are at increased risk for hypoglycemia because gluconeogenesis and especially ketogenesis are incompletely developed. These factors are accentuated in preterm infants, infants of diabetic mothers, infants with erythroblastosis fetalis, asphyxiated infants, and infants who are small or large for gestational age.

Rozance PJ, Wolfsdorf JI. Hypoglycemia in the newborn. *Pediatr Clin North Am.* 2019;66(2):333–342.

Sperling MA, Menon RK. Differential diagnosis and management of neonatal hypoglycemia. *Pediatr Clin North Am.* 2004;51(3):703–723.

101. What is the definition and management of neonatal hypoglycemia?

The definition of hypoglycemia during the first 24 hours of life varies with postnatal age because of the physiologic/metabolic transition that occurs during that time. Fig. 11.7 represents guidelines established by the AAP Committee on Fetus and Newborn.


Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants
[(LPT) infants 34-36$^{6/7}$ weeks and SGA (screen 0-24 hrs); IDM and LGA ≥ 34 weeks (screen 0-12 hrs)]
Symptomatic and <40 mg/dL → IV glucose
ASYMPTOMATIC
Birth to 4 hours of age
INITIAL FEED WITHIN 1 hour
Screen glucose 30 minutes after 1st feed
Initial screen <25 mg/dL
Feed and check in 1 hour
<25 mg/dL
IV glucose*
25-40 mg/dL
Refeed/IV glucose* as needed
4 to 24 hours of age
Continue feeds q 2-3 hours
Screen glucose prior to each feed
Screen <35 mg/dL
Feed and check in 1 hour
<35 mg/dL
IV glucose*
35-45 mg/dL
Refeed/IV glucose* as needed
Target glucose screen ≥45 mg/dL prior to routine feeds

*Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5-8 mg/kg per min (80-100 mL/kg per d). Achieve plasma glucose level of 40-50 mg/dL.

Symptoms of hypoglycemia include: Irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.

Fig. 11.7 Algorithm for screening and management of postnatal glucose. (From Adamkin DH; Committee on Fetus and Newborn. Clinical report—postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics.* 2011;127[3]:575-579.)

102. What is the role of 40% dextrose gel in the treatment of neonatal hypoglycemia?

Infants with hypoglycemia are commonly treated with either supplemental enteral formula feedings or an IV dextrose solution. Both can interfere with breastfeeding. Multiple studies have demonstrated the advantages in reversal of hypoglycemia with the use of 40% dextrose (glucose) gel, typically at a dose of 0.5 mL/kg, which is applied to the infant's buccal mucosa with a gauze swab and massaged into the mucosa with a gloved hand. Use of the gel has been shown to reduce the number of admissions to the NICU, reduce the incidence of mother–infant separation, and increase the likelihood of full breastfeeding after discharge without adverse effects or at 2 years' corrected age. Many centers are utilizing 40% dextrose gel as a first-line treatment for neonatal hypoglycemia.

Ter M, Halibullah I, Leung L, Jacobs S. Implementation of dextrose gel in the management of neonatal hypoglycaemia. *J Paediatr Child Health.* 2017;53(4):408–411.

Weston PJ, Harris DL, Battin M, et al. Oral dextrose gel for the treatment of hypoglycemia in newborn infants. *Cochrane Database Syst Rev.* 2016;5:CDC011027.

103. What is the prognosis of infants with hypoglycemia?

There have been few studies looking at the long-term consequences of hypoglycemia in neonates, and many of the studies that do exist in the literature are complicated by confounders such as the lack of a uniform definition of hypoglycemia; incomplete follow-up; and the presence of confounders such as hypoxemia, respiratory distress, and other medically complex conditions. Together these studies suggest that there are both clinical neurologic and MRI sequelae of *symptomatic* hypoglycemia in both term and preterm infants. There is no evidence that infants with "asymptomatic" hypoglycemia are at risk for neurodevelopmental impairment.

Goode RH, Rettiganti M, Li J, et al. Developmental outcomes of preterm infants with neonatal hypoglycemia. *Pediatrics.* 2016;138(6): e 20161424.

Tin W, Brunskill G, Kelly T, Fritz S. 15-year follow-up of recurrent "hypoglycemia" in preterm infants. *Pediatrics.* 2012;130(6): e1497–e1503.

Lucas A, Morley R, Cole TJ, et al. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ.* 1988;297 (6659):1304–1308.

104. What features on physical examination suggest the etiology of hypoglycemia?

- **Macrosomia:** This occurs in infants of diabetic mothers, infants with severe congenital hyperinsulinism, and infants with Beckwith-Wiedemann syndrome. Recall that insulin is a growth factor and that hyperinsulinism leads to macrosomia.
- **Midline defects:** Congenital pituitary deficiency can be associated with midline defects such as cleft lip, cleft palate, single central incisor, and micro-ophthalmia.
- **Micropenis:** Congenital gonadotropin deficiency and possible pituitary abnormalities can cause this condition.
- **Hepatomegaly:** This is associated with glycogen storage diseases and fatty acid oxidation disorders.
- **SGA:** Infants who are SGA (less than tenth percentile) are at risk for both hypoglycemia and polycythemia (which is an independent risk factor for hypoglycemia).

105. What is the differential diagnosis for an infant with hypoglycemia?

The differential diagnosis for hypoglycemia in the newborn period is broad. The most common etiology of hypoglycemia is transient hypoglycemia of the newborn (as part of the normal transition to the ex utero environment). Other etiologies of hypoglycemia include disorders of growth (such as IUGR or infants who are SGA), perinatal asphyxia, endocrine disruption (such as hyperinsulinemia or abnormal cortisol production), hepatic dysfunction, and, lastly, inborn errors of metabolism.

106. Should insulin be used to treat preterm infants with hyperglycemia?

Early neonatal hyperglycemia is common among preterm infants, particularly very-low-birth-weight newborns, who are frequently receiving parenteral glucose infusions. Studies comparing insulin treatment of hyperglycemia with reduction of glucose infusion rates showed no difference in mortality or morbidity, suggesting that the cause of hyperglycemia and not the blood sugar itself may determine the outcome. Furthermore, insulin was found to reduce hyperglycemia in infants, but was associated with an increased risk for death before 28 days of age. Exact indications for use of insulin remain unclear, but it is widely used because of its ability to promote glucose tolerance and enhance growth.

Sinclair JC, Bottino M, Cowett RM. Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. *Cochrane Database Syst Rev.* 2011;10:CD007615.

Morgan C. The potential risks and benefits of insulin treatment in hyperglycaemic preterm neonates. *Early Hum Dev.* 2015; 91(11):655–659.

107. What are the manifestations of hypocalcemia in the neonate?

The major manifestations are **jitteriness** and **seizures**. Other nonspecific signs include lethargy, abdominal distension, and poor oral intake. Finally, hypocalcemia may present with signs such as high-pitched cry, laryngospasm, Chvostek sign (facial muscle twitching on tapping), and Trousseau sign (carpopedal spasm), but these findings are usually absent during the neonatal period.

108. Which neonates are at highest risk to develop hypocalcemia?

Early neonatal hypocalcemia (first 4 days of life)

- Premature infants
- Perinatal hypoxia-ischemia
- IUGR
- Infants of diabetic mothers
- Maternal anticonvulsant use

Late neonatal hypocalcemia (after the end of the first week of life)

- Hyperphosphatemia
- Hypomagnesemia
- Vitamin D deficiency
- Intestinal malabsorption
- Neonatal hypoparathyroidism
- Furosemide use

- Decreased ionized fraction of calcium (with either normal or decreased total calcium)
    - Citrate (exchange transfusion)
    - Increased free fatty acid levels (intralipid)
    - Alkalosis

109. When should hypocalcemia be treated in the neonate?

Hypocalcemia should be treated when an infant is **symptomatic** or when **the total serum calcium level is <7.0 mg/dL**. Thresholds for treatment based on ionized calcium levels vary between medical centers because of different measurement technologies.

110. How should symptomatic hypocalcemia be treated?

The first line of therapy generally consists of increasing the amount of calcium in the IV infusion to achieve 20 to 75 mg/kg per day of elemental calcium and evaluating serum levels every 6 to 8 hours. After normal calcium levels are achieved, the IV dose can be weaned over 2 to 3 days. The use of a bolus of IV calcium (10% calcium gluconate, 2 mL/kg) over 10 minutes should be reserved for the infant with seizures. In the asymptomatic infant, hypocalcemia most frequently resolves spontaneously without the need for further therapy.

111. What are the causes of neonatal hypomagnesemia?

- Hypocalcemia
- Hyperphosphatemia
- IUGR
- Maternal diabetes
- Intestinal malabsorbtion and urinary losses
- Loop and thiazide diuretics

112. In which neonates should the serum magnesium concentration be measured?

- Any hypocalcemic infant who is not responding to calcium therapy
- Hypotonic infants born to mothers who received magnesium sulfate therapy before delivery
- Infants with seizures of unknown etiology

113. How is hypomagnesemia treated?

Hypomagnesemic infants should be treated with 50% magnesium sulfate, 0.05 to 0.1 mL/kg, given intramuscularly (IM) or by slow IV infusion over 20 minutes. Magnesium levels are followed and the dosage repeated, if necessary.

NEUROLOGIC ISSUES

114. After a difficult delivery, what three major forms of extracranial hemorrhage can occur?

- Caput succedaneum
- Cephalhematoma
- Subgaleal hemorrhage

  Fig. 11.8 and Table 11.6 characterize the major forms of extracranial hemorrhages.

  From Volpe JJ, ed. *Neurology of the Newborn*. 5th ed. Philadelphia, PA: W.B. Saunders; 2008:960.

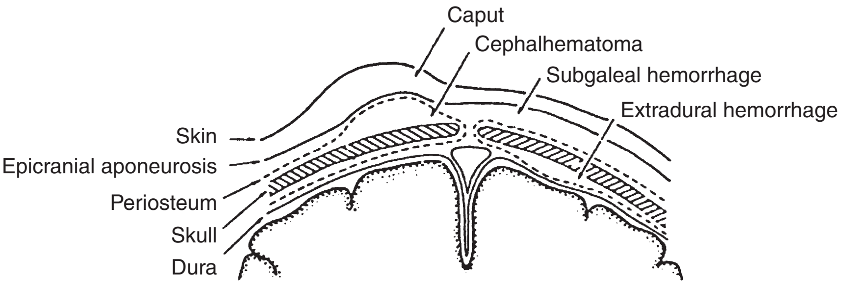


Fig. 11.8 Major forms of extracranial hemorrhage. (From Volpe JJ, ed. *Neurology of the Newborn*. 5th ed. Philadelphia, PA: W.B. Saunders; 2008:960.)

Table 11.6 Major Varieties of Traumatic Extracranial Hemorrhage

LESION	FEATURES OF EXTERNAL SWELLING	INCREASES AFTER BIRTH	CROSSES SUTURE LINES	MARKED ACUTE BLOOD LOSS
Caput succedaneum	Soft, pitting	No	Yes	No
Subgaleal hemorrhage	Firm, fluctuant	Yes	Yes	Yes
Cephalhematoma	Firm, tense	Yes	No	No

From Volpe JJ, ed. *Neurology of the Newborn.* 5th ed. Philadelphia, PA: Saunders; 2008:960.

115. If a cephalhematoma is suspected, should a skull radiograph be performed to evaluate for fracture?

Cephalhematomas occur in up to 2.5% of live births. In studies, the incidence of associated fractures ranges from 5% to 25%. These fractures are almost always linear and nondepressed and do not require treatment. Thus in an asymptomatic infant with a cephalhematoma over the convexity of the skull and without suspicion of a depressed fracture, radiographic imaging is not necessary. If the examination suggests cranial depression or neurologic signs are present, radiographic imaging is warranted.

116. At what gestational age does pupillary reaction to light develop?

Pupillary reaction to light may appear **as early as 29 weeks** into gestation, but is not consistently present **until about 32 weeks**.

117. How does postmaturity differ from dysmaturity?

- *Postmature:* An infant born of a postterm pregnancy (>42 weeks of gestation)
- *Dysmature:* Features of placental insufficiency are present (e.g., loss of subcutaneous fat and muscle mass; meconium staining of the amniotic fluid, skin, and nails)

118. What is the chance that an extremely preterm infant will survive without significant impairment?

As antenatal care and neonatal intensive care improved over the last 30 to 40 years, survival rates for extremely preterm infants improved dramatically. At birth, the most important prognostic factor is gestational age. Additional factors, such as gender, birth weight, use of antenatal steroids, and multifetal gestations, all affect the chances of healthy survival among preterm infants. Although these factors are used to help parents make early treatment decisions, the course during the NICU stay will also influence the infant's long-term outcome. Neurodevelopmental impairment includes varying levels of severity of cerebral palsy (CP), vision impairment, sensorineural hearing loss, developmental delays, and mental retardation. A prospective observational study from Australia examining 751 infants born <28 weeks' gestation in 1991–1992, 1997, and 2005 found that 73% survived to 8 years of age. Of the survivors, 17% had a major disability. Long-term major disability is increased by grade III/IV IVH, periventricular leukomalacia, early postnatal corticosteroid use, bacteremia or fungemia, CNS infections, medical or surgical NEC, and surgery. Of the survivors who had no major postnatal event during the newborn period (about one-half of the group), only 7% had a major disability.

Cheong JLY, Lee KJ, Boland RA, et al. Changes in long-term prognosis with increasing postnatal survival and the occurrence of postnatal morbidities in extremely preterm infants offered intensive care: a prospective observational study. *Lancet Child Adolesc Health.* 2018; 2(12):872–879.

119. Which infants require ophthalmologic evaluation for ROP?

The AAP recommends screening for ROP in all neonates with a birth weight of ≤1500 g or a gestational age of <30 weeks *and* those selected infants weighing between 1500 and 2000 g or >30 weeks' gestation who have had unstable clinical courses, including those requiring cardiorespiratory support, placing them at increased risk.

Fierson WM. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics.* 2018;142(6):e20183061.

120. What are the stages of ROP?

- **Stage I:** Line of demarcation separates vascular and avascular retina
- **Stage II:** Ridging of line of demarcation as a result of scar formation (Fig. 11.9A)
- **Stage III:** Extraretinal fibrovascular proliferation present
- **Stage IV:** Subtotal retinal detachment as extraretinal fibrovascular proliferation contracts (Fig. 11.9B)
- **Stage V:** Complete retinal detachment

The stage of ROP can be modified with the designation of "plus disease," which refers to active inflammation, if there is abnormal dilatation and tortuosity of the posterior retinal vessels. This designation increases the risk for progression of ROP.

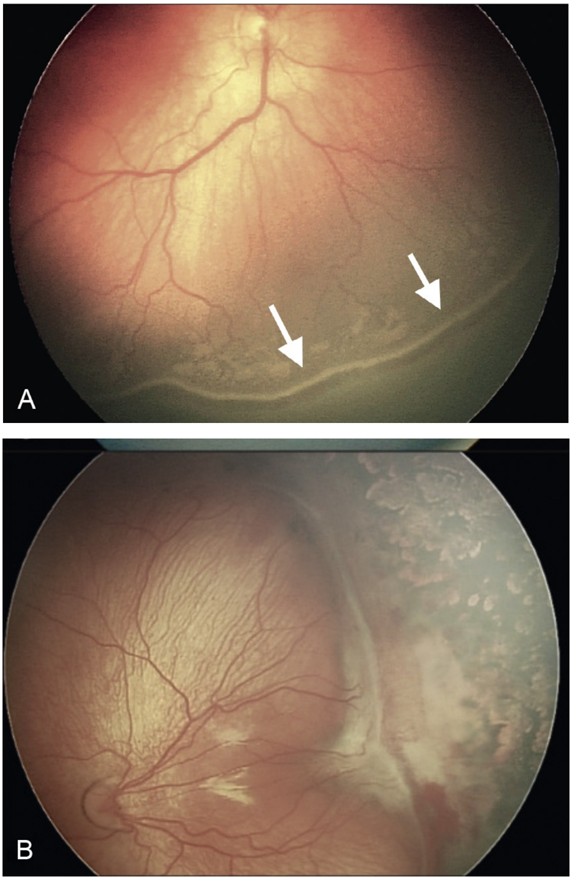


Fig. 11.9 (A) Stage 2 ROP demonstrates an elevated mesenchymal ridge *(arrows)* with highly arborized blood vessels from the vascularized retina diving into the ridge. (From Yanoff M, Duker JS, eds. *Ophthalmology*. 5th ed. Philadelphia, PA: Elsevier;2018:539.) (B) Stage 4 ROP shows retinal detachment, which spares the fovea, the small central area responsible for sharp vision. (From Yanoff M, Duker JS, eds. *Ophthalmology*. 5th ed. Philadelphia, PA: Elsevier;2018:539.)

121. What are the indications for the treatment for ROP?

Based on the results of the Early Treatment for Retinopathy of Prematurity randomized trial, treatment should be initiated for the following retinal findings:

- **Zone I ROP:** Any stage with plus disease
- **Zone I ROP:** Stage III with no plus disease
- **Zone II ROP:** Stage II or III with plus disease

Zones are defined by the location on the retina in relation to the optic disc (ranging from central zone (I) to the periphery (III). Standard treatment is with laser photocoagulation, which obliterates the retina peripheral to the area of vessel development. Improved short-term ophthalmologic outcomes have been demonstrated when intravitreal bevacizumab (Avastin) is used instead of laser therapy for ROP in Zone 1 with plus disease, but longer-term outcomes of this therapy remain unclear.

Fierson WM. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics.* 2018;142(6):e20183061.

Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol.* 2003;121(12):1684–1694.

122. If maternal drug abuse is suspected, which specimen from the infant is most accurate for detecting exposure?

Although urine has traditionally been tested when maternal drug abuse is a possibility, **meconium** has a greater sensitivity than urine and positive findings that persist longer. It may contain metabolites gathered over as much as 20 weeks compared with urine, which represents more recent exposure. Umbilical cord tissue has been proposed as an alternative specimen, as it is as equally sensitive in the detection of some fetal drug exposures as meconium, which in some cases may be passed in utero and in others not for several days.

Colby JM. Comparison of umbilical cord tissue and meconium for the confirmation of in utero drug exposure. *Clin Biochem.* 2017; 50(13–14):784–790.
Wright TE. Biochemical screening for in utero drug exposure. *Drug Metab Lett.* 2015;9(2):65–71.

123. What are the manifestations of drug withdrawal in the neonate?

The signs and symptoms of drug withdrawal in the neonate can be remembered by using the acronym **WITHDRAWAL**:

- **W**akefulness
- **I**rritability
- **T**remulousness, temperature variation, tachypnea
- **H**yperactivity, high-pitched persistent cry, hyperacusis, hyperreflexia, hypertonus
- **D**iarrhea, diaphoresis, disorganized suck
- **R**ub marks, respiratory distress, rhinorrhea
- **A**pneic attacks, autonomic dysfunction
- **W**eight loss or failure to gain weight
- **A**lkalosis (respiratory)
- **L**acrimation

Committee on Drugs. Neonatal drug withdrawal. *Pediatrics.* 1983;72(6):896.

124. What is the recommended pharmacologic treatment for neonatal abstinence syndrome (NAS) from opioid withdrawal?

Unfortunately there is no nationally accepted, evidence-based treatment protocol. There are commonly utilized therapies—an opioid (oral morphine solution, oral methadone, or sublingual buprenorphine) as the initial drug of choice, with phenobarbital or clonidine as second-line therapy—but there is no consensus about which initial treatment is best and what is the most ideal way to taper the medication. Evidence suggests that the use of a standardized protocol for the treatment of NAS may be equally as important as the choice of medication.

Disher T, Gullickson C, Singh B, et al. Pharmacological treatments for neonatal abstinence syndrome: a systematic review and network meta-analysis. *JAMA Pediatr.* 2019;173(3):234–243.
McQueen K, Murphy-Oikonen J. Neonatal abstinence syndrome. *N Engl J Med.* 2016;375(25):2468–2479.

125. Should breastfeeding be initiated in infants with NAS?

Yes, with exceptions. The AAP recommends that neonates prenatally exposed to maternal oral maintenance therapy medications, especially buprenorphine and methadone, be breastfed because these infants have a lower incidences of NAS and require shorter pharmacotherapy compared with infants who are not breastfed. Breastfeeding should be discouraged for mothers who are taking illicit drugs (including marijuana) as detected by history or maternal urine toxicology screens, are involved in polydrug abuse, are not willing to utilize substance abuse disorder treatment, are infected with HIV or hepatitis C, did not have prenatal care, or are taking a medication that is contraindicated with breastfeeding.

Jansson LM, Patrick SW. Neonatal abstinence syndrome. *Pediatr Clin North Am.* 2019;66(4):353–367.
Wu D, Carre C. The impact of breastfeeding on health outcomes for infants diagnosed with neonatal abstinence syndrome. *Cureus.* 2018;10(7):e3061.

126. Does in utero exposure to selective serotonin reuptake inhibitors (SSRIs) result in neonatal withdrawal?

SSRIs are being prescribed with increasing frequency to pregnant women with depression. Recent data suggest that within days of birth, infants experience withdrawal symptoms, including irritability, crying, hypertonia, and seizures. The drug that figures most prominently is paroxetine (Paxil), but similar symptoms have been reported with fluoxetine (Prozac), sertraline (Zoloft), and citalopram (Celexa).

Alwan S, Friedman JM, Chambers C. Safety of selective serotonin uptake inhibitors in pregnancy: a review of current evidence. *CNS Drugs.* 2016;30(6):499–515.
Sanz EJ, De-las-Cuevas C, Kiuru A, et al. Neonatal withdrawal symptoms after in utero exposure to selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet.* 2005;365(9458):482–487.

127. When screening for IVH, when is the best time to perform an ultrasound?

In a series of infants studied by ultrasonography, about 50% had the onset of hemorrhage on the first day of life, 25% on the second day, and 15% on the third day. Thus a single scan on the fourth day of life would be expected to detect more than 90% of IVHs. However, about 20% to 40% of hemorrhages show evidence of extension within 3 to 5 days after initial diagnosis, and thus a second scan is indicated to take place about 5 days after the first to determine the maximal extent of hemorrhage.

128. What is the standard grading system for IVH?

- **Grade I:** Germinal matrix hemorrhage only
- **Grade II:** IVH without ventricular dilation
- **Grade III:** IVH with ventricular dilation
- **Grade IV:** Grade III hemorrhage plus intraparenchymal involvement

Some authorities have abandoned the grade IV classification in favor of “periventricular hemorrhagic infarction” to emphasize that these lesions have a different pathophysiology and are not simply extensions of germinal matrix or IVH into parenchymal tissue. As such, the extent of parenchymal involvement, rather than the grade of hemorrhage, is more important for determining prognosis.

129. What is the cause of hydrocephalus after an intracranial hemorrhage?

The acute hydrocephalus is believed to be a result of impairment of CSF absorption by the arachnoid membrane caused by the particulate blood clot. In subacute or chronic hydrocephalus, ventricular enlargement is the result of an *obliterative arachnoiditis* (likely a chemical inflammatory response from the continued presence of blood), which usually causes a communicating hydrocephalus. Less commonly, obstruction of the aqueduct of Sylvius can lead to a noncommunicating hydrocephalus.

130. What factors predispose premature infants to the development of PVL?

PVL occurs primarily in the distribution of the end zones of deep penetrating arteries resulting in both focal (e.g., cysts) and more diffuse injury to white matter near the trigone of the lateral ventricles and around the foramen of Monro. Predisposing factors include the following:

- **Cerebral ischemia** secondary to disease processes, such as perinatal asphyxia, systemic hypotension, and hypocarbia. Impaired cerebrovascular autoregulation and a pressure-passive cerebral circulation contribute to this kind of injury
- **Infection and inflammation** due to intrauterine infection and fetal inflammatory responses, resulting in the production of cytokines, excitotoxic molecules, and reactive oxygen and nitrogen species, which injure preoligodendrocytes.

131. What imaging studies are used to detect PVL?

The most common imaging technique used in the NICU is ultrasound, which is capable of detecting cystic PVL. However, because overt cysts, which represent focal necrosis, are seen in only 3% or less of preterm infants, MRI must be used to detect abnormal white matter signal, which may be seen in 50% to 80% of preterm infants at term equivalent. These abnormal white matter signals correspond to only a minimal level of severity; however, even mild changes may be associated with neurocognitive abnormalities.

Hinojosa-Rodriguez M, Harmony T, Carrillo-Prado C, et al. Clinical neuroimaging in the preterm infant: diagnosis and prognosis. *Neuroimag Clin.* 2017;16:355–368.

132. What is the most common brachial plexus palsy?

Erb palsy (Fig. 11.10). Neonatal brachial plexus injuries occur in $<0.5\%$ of deliveries and are often associated with shoulder dystocia and breech or forceps delivery.

- Involves upper plexus (C5, C6)
- C7 affected in 50% of cases
- Arm held limply adducted, internally rotated, and pronated with wrist flexed and fingers flexed (“waiter’s tip” position)
- Biceps reflex absent, Moro reflex with hand movement but no shoulder abduction, palmar grasp present
- Ipsilateral diaphragmatic involvement in 5%

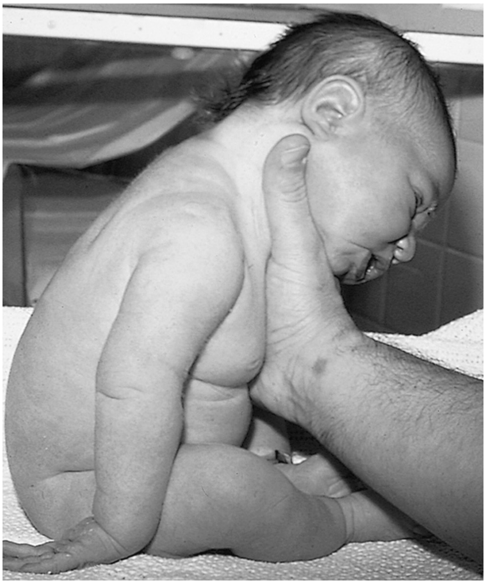


Fig. 11.10 Erb palsy. Newborn demonstrating characteristic posture with the right arm limply adducted and internally rotated. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis.* 5th ed. Philadelphia, PA: Mosby; 2007:45.)

133. What is Klumpke paralysis?

A brachial plexus palsy involving injury to the *lower plexus* (C8, T1). It is associated with weakness of the flexor muscles of the wrist and the small muscles of the hand (“claw hand”). Up to one-third of these patients have an associated Horner syndrome (i.e., constricted pupil, drooping eyelid [ptosis], localized absence of sweating [anhidrosis], and sunken appearance to the eye [enophthalmos]) on the affected side.

134. In newborns with facial paralysis, how is peripheral nerve involvement distinguished from central nerve involvement?

- **Peripheral:** This usually results from compression of the peripheral portion of the nerve by prolonged pressure from the maternal sacral promontory. The use of forceps alone is not thought to be an important causative factor. Peripheral paralysis is unilateral. The forehead is smooth on the affected side, and the eye is persistently open.
- **Central:** This type often results from contralateral CNS injury (temporal bone fracture and/or posterior fossa hemorrhage or tissue destruction). It involves only the lower half or two-thirds of the face; the forehead and eyelids are not affected.

In both forms of paralysis, the mouth is drawn to the normal side when crying, and the nasolabial fold is obliterated on the affected side.

135. Is ankle clonus normal in the newborn infant?

Bilateral ankle clonus of 5 to 10 beats may be a normal finding, especially in infants who are crying, hungry, or jittery. This is particularly true if the clonus is not accompanied by other signs of upper motor neuron dysfunction and is not asymmetrical. Clonus should disappear at about 3 months of age.

136. What are the benefits of therapeutic hypothermia?

In term or near-term (>36 weeks' gestation) newborn infants with a history of a hypoxic-ischemic insult and encephalopathy, the use of therapeutic hypothermia has been shown to decrease the incidence of death or neurodevelopmental impairment at 18 months of age from approximately 61% to 46%. The improvement in neurodevelopment has also been seen in mid-childhood, with improved IQ scores in infants treated with hypothermia.

Lemyre B, Chau V. Hypothermia for newborns with hypoxic-ischemic encephalopathy. *Paediatr Child Health.* 2018;23(4):285–291.

137. When should therapeutic hypothermia be initiated?

In experimental animals, hypothermia is most effective when initiated as soon as possible after the insult. A somewhat arbitrary time frame of 6 hours from birth has been used in clinical trials, because the greatest benefit was observed in experimental animals cooled within 6 hours of the insult. The National Institutes of Health (NIH) is investigating whether the use of hypothermia after 6 hours is also beneficial.

138. What is the best way to initiate therapeutic hypothermia?

Systemic hypothermia is accomplished using a cooling blanket or "cool-cap" device applied to the infant's head. Using either method, the infant's core body temperature is decreased to 93.2°F to 94.1°F (33.5°C to 34.5°C) for a duration of 72 hours. In whole-body cooling, the infant is managed by maintaining the core temperature at approximately 93.2°F (33.5°C), most often with a servo-controlled blanket. In selective head cooling, a water-filled cap is placed on the infant's head at a temperature of 46.4°F to 53.6°F (8°C to 12°C) and the core body temperature is kept at 93.2°F to 95°F (34°C to 35°C) by adjusting the cap temperature and the radiant warmer heat output. Neither method of cooling has been shown to be more effective.

Jacobs SE, Berg M, Hunt R, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev.* 2013;1:CD003311.

Tagin MA, Woolcott CG, Vincer MJ et al. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. *Arch Pediatr Adolesc Med.* 2012;166(6):558–566.

139. Which infants should be treated with therapeutic hypothermia?

Therapeutic hypothermia is indicated for term or near-term (>35 weeks' gestation) infants who show **signs of encephalopathy after an acute hypoxic-ischemic event** near the time of birth. Standard criteria include the following.

- Gestational age ≥36 weeks
- Apgar scores at or below 5 at 10 minutes after birth
- Need for resuscitation at 10 minutes of life
- Cord pH or arterial blood pH ≤ 7.0
- Base deficit of equal to or greater than 16 meq/L within 1 hour of birth
- Evidence of moderate to severe encephalopathy

140. How is neonatal encephalopathy evaluated and classified?

In 1976, Sarnat and Sarnat developed a staging system for the neurologic findings seen after a perinatal hypoxic-ischemic insult. The system included three stages that were assigned based on findings in several categories: level of consciousness, neuromuscular control, complex reflexes, autonomic function, seizures, and electroencephalogram (EEG) findings. A modified version of this staging system was used as the basis for the neurologic evaluation of infants enrolled in the therapeutic hypothermia trials. For details of a modified Sarnat score, see Table 11.7.

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electrocardiographic study. *Arch Neurol.* 1976;33(10):696–705.

Table 11.7 Characteristics of the Three Stages of Neonatal Encephalopathy

	STAGE 1	STAGE 2	STAGE 3
Level of Consciousness	Hyperalert	Lethargic or obtunded	Stupor
Neuromuscular Tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Primitive Reflexes	Weak suck Strong Moro	Weak or absent suck Weak or incomplete Moro	Absent suck Absent Moro
Deep Tendon Reflexes	Hyperactive	Hyperactive	Decreased or absent
Autonomic Function	Dilated pupils Tachycardia	Constricted pupils Bradycardia	Deviated, dilated or nonreactive Variable HR
Seizures	Absent	Common	Variable

HR, Heart rate.

Modified from Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol.* 1976;33(10):696–705.

141. When should hearing evaluations be repeated after NICU discharge?

Even those who pass the universal newborn hearing screen in the NICU should have a diagnostic hearing evaluation **at 24 to 30 months of age** if any risk factors for progressive sensorineural (SN) hearing loss are present. These risk factors include a NICU stay of ≥5 days, treatment with extracorporeal membrane oxygenation (ECMO), assisted ventilation, ototoxic antibiotics (such as aminoglycosides), loop diuretics, or therapy with exchange transfusion for hyperbilirubinemia.

Wroblewska-Seniuk KE, Dabrowski P, Szyfter W, Mazela J. Universal newborn hearing screening: methods and results, obstacles, and benefits. *Pediatr Res.* 2017;81(3):415–422.

Harlor AD Jr, Bower C. Hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics.* 2009;124(4):1252–1263.

NUTRITION

142. How many calories are required daily for growth in a healthy, growing preterm infant?

Preterm infants need about **120 cal/kg per day** from enteral feeds. About 45% of the caloric intake should be carbohydrate, 45% should be fat, and 10% should be protein. Infants who expend increased calories (e.g., those with chronic lung disease, fever, or cold stress) may need a higher daily caloric intake.

143. How should enteral feedings be started in the preterm infant?

Initiation of feedings in preterm infants frequently depends on their cardiorespiratory stability. There is great variability from study to study on the definition of “early” feedings ranging from 1 to 8 days of life. Trophic feedings (minimal enteral feeds) generally consist of breast milk or preterm infant formula at a volume of 12 to 24 mL/kg per day. Trophic feedings are generally begun in the first few days of life. If trophic feedings are well tolerated for at least 2 days, feedings should be advanced. The safest rate of feeding advancement is controversial. In retrospective studies a higher rate of feeding advancement was associated with a greater risk for NEC. Therefore many centers are cautious during the first few days of feeding advancement and choose a rate of advancement of 20 mL/kg per day. If feeding advancements are being tolerated, the rate of feeding advancement can be increased to 30 to 35 mL/kg per day until a volume of 140 to 160 mL/kg per day is achieved. Prospective clinical trials have demonstrated the safety of that approach.

Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. *Cochrane Database Syst Rev.* 2013;3:CD000504.

Tyson JE, Kennedy KA, Lucke JF, Pedroza C. Dilemmas initiating enteral feedings in high risk infants: how can they be resolved? *Semin Perinatol.* 2007;31(2):61–73.

Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database Syst Rev.* 2017;8:CD001241.

144. What are the medical benefits of breastfeeding?

Proven benefits

- Decreased incidence of otitis media, respiratory tract infections, and gastrointestinal illness
- Decreased incidence of neonatal sepsis and NEC in preterm infants
- Decreased risk for SIDS
- Decreased risk for developing asthma
- Improved neurodevelopmental outcomes, especially in preterm infants
- Decreased incidence of diabetes mellitus and obesity

American Academy of Pediatrics. Policy Statement: Breastfeeding and the use of human milk. *Pediatrics.* 2012;129(3):e827–e841.

Hoddinott P, Tappin D, Wright C. Breast feeding. *BMJ.* 2008;336:881–887.

La Leche League. www.llli.org. Accessed January 20, 2020.

145. How does the composition of maternal breast milk differ for a full-term versus a premature baby?

The composition of human milk for preterm infants (26 to 36 weeks’ gestation) differs from that for term infants in a number of ways. For every 100 mL, it is initially higher in calories, protein, fat, free amino acids, and sodium. Preterm milk is also higher in bioactive molecules, including cytokines, growth factors, and lactoferrin. One nutritional exception is calcium, which is significantly lower in preterm milk than term milk. However, after the first few weeks after delivery when breast milk becomes mature, many of the nutritional advantages of preterm milk are lost.

Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. *BMC Pediatr.* 2014;14(1):216.

Underwood MA. Human milk for the preterm infant. *Pediatr Clin North Am.* 2013;60(1):189–207.

146. How does colostrum differ from mature human breast milk?

Colostrum is the thick, yellowish mammary secretion that is characteristic of the first postpartum week. It is higher in phospholipids, cholesterol, and protein concentration and lower in lactose and total fat composition than mature breast milk. Colostrum is particularly rich in immunoglobulins, especially secretory IgA.

147. How do fore milk and hind milk differ?

The caloric density of human milk increases in a nonlinear fashion while the infant is breastfeeding. *Hind milk* (produced at the end of the feeding) can have a fat content that is 50% higher than *fore milk*. In preterm infants with poor weight gain, hind milk may offer a nutritional advantage.

148. What are contraindications to breastfeeding?

- **Inborn errors of metabolism:** Galactosemia, phenylketonuria, and urea cycle defects
- **Infections**:
  - Mothers with human T-cell lymphotropic virus (HTLV) types I and II or Ebola virus.
  - Mothers with active tuberculosis or brucellosis (before treatment), peripartum development of varicella (5 days before delivery to 2 days after delivery), and herpes simplex (when lesions are present on the breast).
  - In the industrialized world, it is not recommended that HIV-positive mothers breastfeed. In the developing world, the risks for malnutrition and infectious diseases may outweigh the risk for acquiring HIV from breastfeeding. However, the World Health Organization still advises any promotion of breastfeeding should be done in conjunction with the provision of maternal antiretroviral interventions to prevent transmission.
- **Substance abuse or use:** Cocaine, stimulants, marijuana, or other illicit drugs
- **Medications:** Sulfonamides (for ill, stressed, or preterm infants or infants with hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency), radioactive medicines, chemotherapeutic agents (alkylating agents), bromocriptine (suppresses lactation), and lithium (in general, psychotropic drugs should be used with caution). Most other medications are compatible with breastfeeding, or suitable substitutes exist.

Arikawa S, Rollins N, Jourdain G, et al. Contribution of maternal antiretroviral therapy and breastfeeding to 24-month survival in human immunodeficiency-exposed uninfected children: an individual pooled analysis of African and Asian studies. *Clin Infect Dis.* 2018; 66(11):1668–1677.

American Academy of Pediatrics. Policy Statement: breastfeeding and the use of human milk. *Pediatrics.* 2012;129(3):e827–e841.

149. What advice should be given to a mother who plans to express and save breast milk for later feedings?

Ideally, milk should be collected as cleanly as possible and then stored rapidly at 37.4°F to 39.2°F (3°C to 4°C) or colder within 4 to 6 hours; the milk should be used within 5 days. Alternatively, breast milk can be frozen and stored for about 6 months. After the milk has thawed, it should not be refrozen.

150. What interventions for mothers of preterm infants help sustain milk production through 40 weeks' gestation?

- Initiation of expression of milk by 6 hours postdelivery
- Expression of milk >5 times per day
- Double-pumping (pumping both breasts simultaneously)
- Kangaroo care (holding a naked or partially dressed infant against a mother's bare skin for as long as possible each day)

Fewtrell M, Kennedy K, Ahluwalia JS, et al. Predictors of expressed breast milk volume in mothers expressing milk for their preterm infant. *Arch Dis Child Fetal Neonatal Ed.* 2016;101(6):F502–F506.

151. What are the benefits of donor breast milk compared with preterm formula?

As benefits of human breast milk are increasingly understood, use of pasteurized donor human milk has been implemented in many NICUs globally. A 2016 controlled trial of 363 infants showed no difference in neurodevelopmental outcomes between infants fed with donor breast milk versus preterm formula, but did find a decreased incidence of NEC in the donor breast milk–fed infants. There is some concern that use of donor breast milk leads to impaired growth, but studies have been confounded by varying use of mother's own milk and fortification. The safety and efficacy of donor breast milk for preterm infants are being investigated by the Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD) (MILK trial).

Corpeleijn WE, De Waard M, Christmann V, et al. Effect of donor milk on severe infections and mortality in very low-birth-weight infants: the early nutrition study randomized clinical trial. *JAMA Pediatr.* 2016;170(7):654–661.

O'Connor D, Gibbens S, Kiss A, et al. Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 19 months: a randomized clinical trial. *JAMA.* 2016;316(18):1897–1905.

152. What are the advantages of a 60/40 whey-to-casein ratio in infant formulas?

The term 60/40 refers to the percentage of whey (lactalbumin) and casein in human milk or cow milk formulas. This ratio makes for small curds and therefore easy digestibility by the infant. The 60/40 ratio is of particular advantage to the preterm infant because it is associated with lower levels of serum ammonia and a decreased incidence of metabolic acidosis. Only human milk or formulas that supply protein in this ratio provide adequate amounts of the amino acids cystine and taurine, which may be essential for the preterm infant.

153. "Low-iron" or "regular iron-fortified" formulas: which are preferred for infants?

"Low-iron" formulas contain 4 to 6 mg/L of elemental iron, whereas iron-fortified formulas have 12 mg/L. Infants who are not breastfed should receive iron-fortified formula. Although a greater percentage of iron is absorbed from the ingested low-iron formula, the quantity may not be sufficient to protect against the development of iron-deficiency anemia. In addition, despite anecdotal experiences, the incidence of colic, constipation, vomiting, and fussiness does not vary among infants fed the two formulas. The AAP recommends that all formula fed to infants be iron fortified.

American Academy of Pediatrics. Iron fortification of infant formulas. *Pediatrics*. 1999;104(1 Pt 1):119–123.

154. Is vitamin D supplementation necessary for exclusively breastfed term infants?

The following recommendations have been made by the AAP:

- Beginning in the first 2 months of life, all breastfed infants should be supplemented with 400 IU per day of vitamin D to prevent the occurrence of rickets.
- Malnourished mothers may need to supplement their breastfed babies with multivitamins.
- Mothers who are strict vegetarians may have low concentrations of B vitamins in their breast milk, and infants may need supplementation with vitamin B_{12}.

Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children and adolescents. *Pediatrics*. 2008;122(5):1142–1152.

155. Which fatty acids are essential for the neonate?

Humans cannot synthesize fatty acids with double bonds in the omega-6 and omega-3 positions. Therefore **linoleic acid** (omega-6) and **linolenic acid** (omega-3) must be provided in the diet to serve as precursors for fatty acids with these bonds. In infants weighing $<$1750 g who experience delay in or difficulty with maintaining full enteral feedings, **arachidonic** and **docosahexaenoic (DHA) acids** may also be essential. These fatty acids are vital for normal brain development, myelination, cell proliferation, and retinal function.

156. What are the proven advantages of supplementing formulas with long-chain polyunsaturated fatty acids (LCPUFA)?

- DHA-supplemented infants transiently demonstrate higher behaviorally and electrophysiologically based measurements of visual acuity.
- The beneficial effects of LCPUFA supplementation on visual acuity and cognitive development are inconsistent in meta-analyses but appear more compelling in preterm infants. The meta-analysis is compromised by the heterogeneity in dose, source, and composition of fatty acid supplementation.

Jasani B, Simmer K, Patole SK, Rao SC. Long chain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database Syst Rev.* 2017;3:CD000376.

Moon K, Rao SC, Schulzke SM, et al. Long chain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev.* 2016;12:CD000375.

157. What are the manifestations of essential fatty acid deficiency?

Scaly **dermatitis**, **alopecia**, **thrombocytopenia** (and platelet dysfunction), **failure to thrive**, and increased susceptibility to **recurrent infection**. To prevent and treat fatty acid deficiency, 4% to 5% of caloric intake should be provided as linoleic acid and 1% as linolenic acid. This requirement can be met by 0.5 to 1.0 g/kg per day of IV lipids.

158. What morbidities (short and long term) are known to occur more frequently in growth-restricted babies?

- *Short-term morbidities:* Perinatal asphyxia, meconium aspiration, fasting hypoglycemia, alimented hyperglycemia, polycythemia-hyperviscosity, NEC, and immunodeficiency
- *Long-term morbidities:* Poor developmental outcome and altered postnatal growth

Most studies demonstrate decreased cognitive function and increased rates of behavioral problems in both term and preterm infants with IUGR. In term infants with IUGR, there are also increased rates of CP; the literature remains divided about rates of CP in preterm infants with IUGR. Evidence is increasing that the *cause* of an infant's growth restriction (e.g., chromosomal abnormalities versus chronic hypoxia) plays a significant role in the severity of neurodevelopmental outcomes.

Strauss RS. Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British Birth Cohort. *JAMA.* 2000;283(5):625–632.

Kok JH, den Ouden AL, Verloove-Vanhorick SP, Brand R. Outcome of very preterm small for gestational age infants: the first nine years of life. *Br J Obstet Gynecol.* 1998;105(2):162–168.

159. When do premature infants "catch up" on growth charts?

Most catch-up growth takes place **during the first 2 years of life**, with maximal growth rates occurring between 36 and 40 weeks after conception. Little catch-up growth occurs after the chronologic age of 3 years. About 15% of infants born prematurely remain below normal weight at 3 years of age.

RESPIRATORY ISSUES

160. What causes infants to grunt?

Infants with respiratory disease tend to expire through closed or partially closed vocal cords to elevate transpulmonary pressure and increase lung volumes. This results in an improved ventilation-to-perfusion ratio with better gas exchange. It is during the last part of expiration, when gas is expelled through the partially closed vocal cords, that the audible grunt is produced.

161. What can hyperpnea and tachypnea signify in the neonate?

- *Hyperpnea* refers to deep, relatively unlabored respirations at mildly increased rates. It is typical of situations in which there is reduced pulmonary blood flow (e.g., pulmonary atresia), and it results from the ventilation of underperfused alveoli.
- *Tachypnea* refers to shallow, rapid, and somewhat labored respirations, and it is seen in the setting of low lung compliance (e.g., primary lung disease, pulmonary edema).

162. What conventional mechanical ventilator settings are likely to affect PO_2 and PCO_2?

- **Pao_2 is *increased*** by raising the inspired oxygen concentration or the mean airway pressure, which can be accomplished with increases in the PEEP, the PIP, and the inspiratory-to-expiratory ratio.
- **Pco_2 is *decreased*** by increasing minute ventilation, which can be accomplished by increasing the ventilator rate or PIP. An increase in PEEP without an increase in PIP may increase the $Paco_2$ by decreasing the tidal volume.

163. What are the physiologic effects of PEEP?

PEEP can prevent alveolar collapse, maintain lung volume at end expiration, and improve ventilation-perfusion mismatch. However, an increase in PEEP may decrease tidal volume and impede CO_2 elimination. Furthermore, elevations in PEEP to nonphysiologic values may decrease lung compliance, impair venous return, decrease cardiac output, and reduce tissue oxygen delivery.

164. What are the most common causes of respiratory distress in term or late preterm infants?

Respiratory distress after birth is usually identified by the presence of tachypnea (respiratory rate $>$ 65), nasal flaring, chest wall retractions, and hypoxemia. The most common causes of respiratory distress in term or late preterm infants include transient tachypnea of the newborn (TTN), pneumonia, and meconium aspiration syndrome. RDS caused by immature lung development and surfactant deficiency can occur in late preterm or even term infants, but its incidence decreases with advancing gestational age. Pneumothorax can occur in association with other respiratory diseases, but can also occur spontaneously in up to 1% of newborn infants. Spontaneous pneumothorax is frequently asymptomatic and may resolve without any therapy.

165. What are the risks and benefits of oxygen therapy in preterm infants?

Oxygen is a necessary treatment for many preterm infants but may have significant adverse effects. Preterm infants are thought to be at particular risk from excessive oxygen therapy due to immaturity of the antioxidant system. Hyperoxia may therefore lead to increased oxygen free radicals, which in turn lead to increased inflammation, exacerbating the common morbidities associated with prematurity (e.g., BPD, ROP). Historically, preterm infants treated without supplemental oxygen had poorer survival rates than those treated with unrestricted oxygen. However, unrestricted oxygen therapy was found to be associated with ophthalmologic disease leading to blindness. In recent years with the availability of pulse oximetry, large clinical trials have shown that maintaining oxygen saturation at lower (85% to 89%) compared with higher (91% to 95%) levels was associated with higher rates of mortality and NEC but lower rates of ROP. The incidence of blindness was unaffected.

Askie LM, Darlow BA, Finer N, et al. Association between oxygen saturation targeting and death or disability in extremely preterm infants in the Neonatal Oxygenation Prospective Meta-analysis collaboration. *JAMA.* 2018;319(21):2190–2201.

Askie LM, Darlow BA, Davis PG, et al. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database Syst Rev.* 2017;4:CD011190.

Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics.* 2004;113(2):394–396.

166. What is RDS?

RDS is a pulmonary disease of immature lung development and surfactant deficiency. Most frequently seen in preterm infants, the clinical presentation is characterized by signs of respiratory distress, including nasal flaring, tachypnea, and grunting. Infants with severe RDS will develop a significant oxygen requirement with a large alveolar-arterial oxygen difference. Symptoms often present shortly after birth and can increase in severity over the first 48 to 72 hours of life. The radiologic findings of RDS consist of a homogenous ground-glass appearance of the lung fields with visible air bronchograms (Fig. 11.11). The pathophysiology of RDS involves insufficient surfactant stores leading to decreased compliance of the lungs and inability of the infant to maintain air in the lung. This results in tiny areas of collapsed lung (microatelectasis) and reduced functional residual capacity (FRC).

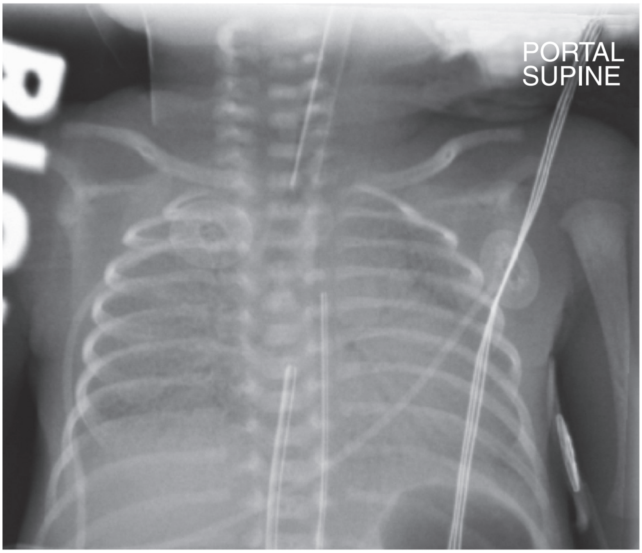


Fig. 11.11 Radiograph showing the typical appearance of respiratory distress syndrome.

167. What is the composition and function of surfactant?

Surfactant is a surface-active lipoprotein complex composed of a mixture of phospholipids (90%), mostly phosphatidylcholine, and proteins (10%) and a small portion of other lipids. The main function of surfactant is to decrease surface tension of the alveoli, which allows for maintenance of FRC and the prevention of atelectasis and lung injury. The surfactant proteins also contribute to natural immunologic defenses and assist with the spreading of surfactant throughout the alveoli and the recycling of surfactant between cells and the airspaces.

168. When is treatment with exogenous surfactant indicated in newborn infants?

Surfactant replacement therapy is indicated for **preterm infants with RDS who have been intubated** or who **require a high oxygen concentration to maintain Spo_2 >90% while on CPAP**. When intubating an infant for surfactant administration, the goal is to attempt extubation quickly after the surfactant has been given. Surfactant treatment may also be beneficial for infants with surfactant inactivation due to meconium aspiration syndrome, pneumonia, or pulmonary hemorrhage.

Polin RA, Carlo WA and Committee on Fetus and Newborn. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics.* 2014;133(1):156–163.

169. What are the characteristics of the “physiologic transition” after birth?

Normal circulatory transition occurs when the infant is born and the umbilical cord is clamped. This removes the placenta from the circuit and increases systemic vascular resistance. When the infant breathes, lungs fill with air and pulmonary vascular resistance decreases, which results in increased pulmonary blood flow and increased pulmonary venous return to the heart. As pulmonary arterial pressure decreases below systemic arterial pressure, blood flow through the patent ductus arteriosus (PDA) transitions from a right-to-left (fetal pattern) to a left-to-right (newborn pattern).

170. What is PPHN?

PPHN is a clinical syndrome of severe hypoxemia that occurs in 1 to 2 per 1000 newborn infants. PPHN results from failure of the fetal circulatory pattern to transition normally to the newborn circulatory pattern. Therefore in infants with PPHN, the normal decline in pulmonary vascular resistance fails to occur. When pulmonary vascular resistance does not decrease as expected, the pulmonary arterial pressure remains elevated, pulmonary blood flow remains low, and some of the right ventricular output is directed right to left across the PDA and foramen ovale. Poorly oxygenated blood is thus shunted to the systemic circulation, leading to significant hypoxemia. In addition to hypoxemia, cardiac output can be compromised. The low pulmonary blood flow leads to decreased left ventricular filling and output. Furthermore, when the right ventricular pressure is higher than the left ventricular pressure, the right ventricle may impair the function of the left ventricle, leading to impaired cardiac output. The clinical syndrome is recognized by labile hypoxemia often accompanied by hemodynamic instability.

171. In what clinical settings does PPHN occur?

PPHN is associated frequently with other illnesses (often respiratory), such as pneumonia, meconium aspiration syndrome, RDS, pulmonary hypoplasia, or sepsis or congenital diaphragmatic hernia (CDH) (see question 172). Most often the pulmonary hypertension improves as the other illness improves, but PPHN can require a significant level of supportive care until recovery. Rare causes of PPHN, such as congenital surfactant deficiencies or alveolar capillary dysplasia, will present similarly and will have associated pulmonary hypertension but are not reversible. Diagnosis of PPHN is made by echocardiography.

172. What is the most common type of CDH?

Bochdalek hernia, which accounts for 90% of all CDHs. This is a posterolateral hernia that most commonly (70% to 90%) occurs on the left side. The usual presentation is at birth with severe cardiorespiratory distress. Examination is characterized by a scaphoid abdomen and decreased breath sounds on the affected side. Radiographs reveal loops of bowel in the thoracic cavity (Fig. 11.12). Bag-mask ventilation should be minimized to avoid abdominal distention.

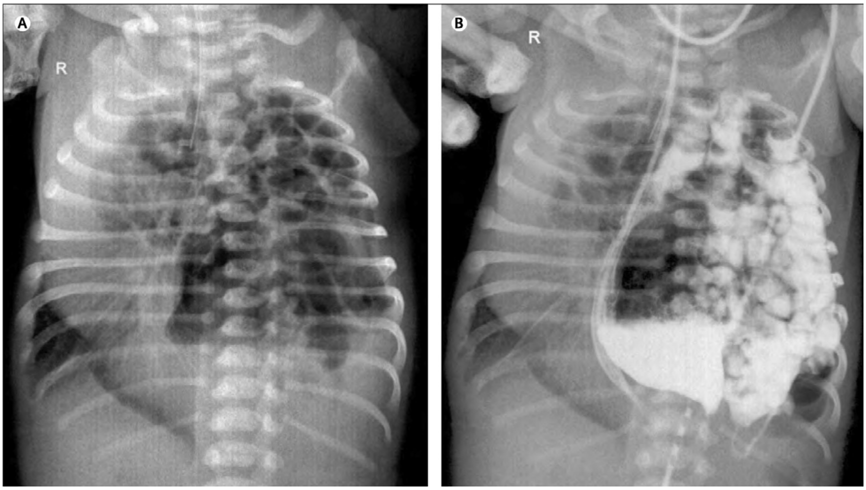


Fig. 11.12 Bochdalek hernia. (A) Chest x-ray shows herniated bowel loops in the left hemithorax and displacement of the mediastinum to the opposite side, severely reducing lung space. (B) Upper gastrointestinal series shows the stomach and bowel loops stained with contrast in the left hemithorax. (From Hu X, Prof BL. *Lancet.* 2018;392[10141]:60.)

173. What is the mechanism of action of inhaled nitric oxide (iNO) in the management of pulmonary hypertension?

Nitric oxide, produced endogenously in endothelial cells at the time of transition from fetal to neonatal life, diffuses to the vascular smooth muscle cell, where it increases the activity of soluble guanylate cyclase. This leads to the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP), which in turn causes smooth muscle relaxation leading to pulmonary vasodilation. Similarly, when exogenous iNO is administered, it diffuses from the alveolus to the smooth muscle cells with similar effects. iNO is then rapidly bound and inactivated by reduced hemoglobin in the vascular space, thus avoiding concomitant reductions in systemic blood pressure.

174. What is the pathophysiology and typical course of TTN?

TTN, also called *retained fetal lung fluid (RFLF) syndrome,* is the most common cause of respiratory distress in newborn infants and is caused by incomplete absorption of fetal lung fluid after birth. The fetal lungs are filled with fluid that is secreted by the pulmonary epithelial cells, which is a critical component to lung development in utero. As the fetus approaches term gestation, the rate of secretion of fluid decreases, and during labor the lung fluid is progressively absorbed via epithelial sodium channels into the interstitial spaces and lymphatics. After birth, the lungs fill with air and any remaining lung fluid is cleared. When birth occurs before term or the infant is delivered by cesarean section, the retained fetal lung fluid may cause respiratory distress. Most frequently, the retained fetal lung fluid continues to be reabsorbed after birth and the signs of respiratory distress (tachypnea, retractions, and grunting) improve within 24 to 48 hours of life. Most infants do not need significant treatment during this time, but some may need oxygen or CPAP to maintain adequate oxygenation and decrease the work of breathing. Chest radiographs of infants with TTN will show streaky parenchymal lung opacities and may have small pleural effusions that improve within hours of birth.

175. Why are fetuses with anhydramnios (complete lack of amniotic fluid) or severe oligohydramnios (a paucity of amniotic fluid) at risk for respiratory problems after birth?

Appropriate lung development relies on the balance between fetal lung fluid secretion and drainage from the lung. The fluid is produced by lung cells and is passively drained from the lung into the amniotic fluid or is swallowed. When the amniotic fluid volume is markedly decreased, lung fluid drains more rapidly, impairing lung development. Therefore fetuses with anhydramnios due to renal disease or early rupture of membranes without reaccumulation of amniotic fluid are at risk for severe pulmonary hypoplasia. The severity of illness in these infants varies and is not always predictable prenatally.

176. What is BPD?

BPD was first described by Northway in 1967 as a pulmonary disease identified after the acute phase of RDS. The disease occurred after a period of treatment with mechanical ventilation and high oxygen concentrations. Clinical features included prolonged need for respiratory support and oxygen, and radiographs displayed alternating areas of lucency (bullae) and opacity (atelectasis) and cardiomegaly. The mortality rate associated with the disease was high. Pathologic findings included diffuse inflammatory changes, emphysematous alveolar changes, fibrotic changes, vascular changes consistent with pulmonary hypertension, and abnormal lymphatics. The pathogenesis of BPD has been attributed to ventilator- and oxygen-induced lung injury. However, the preterm immature lung is particularly susceptible to lung injury, and therefore lung immaturity itself plays a significant role in the development of lung disease.

Northway WH, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. *N Engl J Med.* 1967;276:357–368.

177. What is “new BPD”?

As respiratory care and survival rates of preterm infants have improved over recent years, BPD has been identified in a somewhat different form. “New BPD” is a disease of lower-gestational-age premature infants who initially may require minimal levels of respiratory support. The pathologic hallmarks of new BPD are developmental arrest of the lung with alveolar simplification and reduced septation, rather than diffuse inflammation and fibrosis.

Jobe AJ. The new bronchopulmonary dysplasia. *Curr Opin Pediatr.* 2011;23(2):167–172.

178. In the current era of neonatal medicine, how is BPD or chronic lung disease (CLD) diagnosed?

BPD has traditionally been identified in maturing preterm infants by the ongoing need for respiratory support, specifically oxygen therapy. The names *bronchopulmonary dysplasia* and *chronic lung disease* have been used in different ways by different individuals and are sometimes used interchangeably. In previous eras of neonatology, BPD was diagnosed in infants treated with oxygen at 28 days of life. As more immature infants survived, the diagnosis shifted to describe infants who required supplemental oxygen at 36 weeks adjusted gestational age. Because the indications for oxygen therapy vary by center with differing target oxygen saturation levels, an alternative “physiologic definition” of BPD was developed. The physiologic definition requires a progressive room air challenge for infants receiving $<$30% oxygen at 36 weeks adjusted age. “No BPD” is defined as a saturation value $\geq$90% in room air, which is maintained for at least 30 minutes. In 2000, an NIH workshop developed a consensus definition for BPD that stratified the severity of disease and has been more predictive of later outcomes than previous definitions. Details of the consensus definition are outlined in Table 11.8.

Walsh MC, Szefler S, Davis J, et al. Summary proceedings from the bronchopulmonary dysplasia group. *Pediatrics.* 2006;117:S52–S56.

Ehrenkrantz RA, Walsh MC, Vohr BR, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics.* 2005;116:1353–1360.

Table 11.8 NIH Consensus Definition of BPD

BPD SEVERITY	RESPIRATORY SUPPORT AT 36 WEEKS ADJUSTED AGE (IF BORN LESS THAN 36 WEEKS’ GA) OR AT 56 DAYS’ POSTNATAL AGE
Treatment with oxygen $>$21% for at least 28 days plus:	
Mild BPD	Breathing room air
Moderate BPD	Need for $<$30% oxygen
Severe BPD	Need for $>$30% oxygen and/or positive pressure (PPV or NCPAP)

BPD, bronchopulmonary dysplasia; *GA*, gestational age; *NCPAP*, nasal continuous positive airway pressure; *PPV*, positive-pressure ventilation.

Modified from Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163(7):1726.

179. Does nasal prong CPAP decrease the risk for BPD?

Yes. Randomized clinical trials in preterm infants with RDS comparing use of CPAP with routine intubation and administration of surfactant demonstrated that early CPAP decreases the need for mechanical ventilation and improves the outcome of survival without BPD. However, when early CPAP is compared with early surfactant without ventilation or with minimal/brief ventilation (INSURE approach), the benefits of CPAP are not as clear. The optimal way to provide CPAP (bubble, variable-flow devices, or ventilator-derived CPAP) is unknown.

Wright CJ, Polin RA. Noninvasive support: does it really decrease bronchopulmonary dysplasis? *Clin Perinatol.* 2016;43(4):783–798.

180. Which infants benefit most from ECMO?

ECMO is prolonged cardiopulmonary bypass that is used to treat newborn infants with *reversible pulmonary disease* that has not adequately responded to conventional management. Although overall survival is about 70% to 80%, it varies by diagnosis, with rates of more than 90% for meconium aspiration syndrome, 75% for sepsis, and about 50% for CDH. Use of iNO has reduced the need for ECMO.

181. What are the benefits of caffeine therapy in preterm infants?

Caffeine has been shown to be an effective treatment for apnea of prematurity. Caffeine's mechanisms of action are at least three fold: enhancing sensitivity to carbon dioxide via adenosine antagonism (adenosine receptors, when stimulated, inhibit inspiration), improving diaphragmatic contractility, and increasing muscle tone. In infants with apnea of prematurity, use of caffeine not only lessens episodes of apnea but also reduces the need for mechanical ventilation when given to facilitate extubation. Compared with placebo, caffeine decreases the risk for BPD and in long-term outcome studies reduced the risk for motor impairment. Little evidence supports early use (<3 days after birth) or prophylactic administration.

Gentle SJ, Travers CP, Carlo WA. Caffeine controversies. *Curr Opin Pediatr.* 2018;30(2):177–181.

Atik A, Harding R, DeMatteo R, et al. Caffeine for apnea of prematurity: effects on the developing brain. *Neurotoxicology.* 2017;58:94–102.

Schmidt B, Roberts RS, Anderson PJ, et al. Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity: an 11-year follow-up of the CAP Randomized Clinical Trial. *JAMA Pediatr.* 2017;171(6):564–572.

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CHAPTER 12

NEPHROLOGY

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ACID–BASE, FLUIDS, AND ELECTROLYTES

1. How do you assess a child with hyponatremia?

The serum sodium concentration, even in states of volume depletion, reflects the extracellular water or volume status. In children presenting with *hyponatremia,* the ***volume status*** must always be evaluated. Volume status may be increased, normal, or decreased. The causes of hyponatremia are as follows:

Dilutional hyponatremia:

- If the urine specific gravity is <1.003, look for causes of *excess free water* administration by taking a careful history: inappropriate oral or intravenous (IV) hypotonic fluid administration in a patient with acute or chronic renal failure who cannot excrete free water maximally, low-solute formulas or plain water in infants, excessive use of tap water in infants with diarrhea or use as enemas, and psychogenic polydipsia.

If none of these causes is present, use the urinary sodium concentration to help categorize the cause of hyponatremia.

Depletional hyponatremia with extrarenal losses:

- *If the patient is hypovolemic and the urinary sodium concentration is <20 mEq/L, the cause is likely to be* gastrointestinal losses (vomiting, diarrhea, drainage tubes, fistulas, gastric drainage), skin losses (cystic fibrosis, heat stroke), or third spacing (burns, pancreatitis, muscle trauma, effusions, ascites, peritonitis).

Depletional with renal losses:

- *If the urine sodium concentration is > 20 mEq/L, the cause is likely to be* diuretics, osmotic diuresis, salt-losing nephritis, mineralocorticoid deficiency, congenital adrenal hypoplasia, or pseudohypoaldosteronism.
- *If the patient is euvolemic and urine sodium concentration is >20 mEq/L,* consider glucocorticoid or thyroid problems, syndrome of excessive antidiuretic hormone (SIADH), and the reset osmostat variant (a possible SIADH variant).
- *If the patient is hypervolemic and the urine sodium concentration is <20 mEq/L*, consider edema-forming states: nephrotic syndrome, congestive heart failure, or liver failure.
- *If the urine sodium concentration is >20 mEq/L*, consider acute kidney injury or chronic renal disease.

Dineen R, Thompson CJ, Sherlock M. Hyponatremia—presentations and management. *Clin Med (Lond).* 2017;17(3):263–269.
Ball SG, Igbal Z. Diagnosis and treatment of hyponatraemia. *Best Pract Res Clin Endocrinol Metab.* 2016;30(2):161–173.
Avner ED. Clinical disorders of water metabolism: hyponatremia and hypernatremia. *Pediatr Ann.* 1995;24(1):23–30.

KEY POINTS: DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA

- Hyponatremia with an elevated serum creatinine suggests renal disease or prerenal hypovolemia with hypotonic fluid ingestion.
- Hyponatremia with high urine osmolality and high urine sodium suggests SIADH.
- Hyponatremia with hyperkalemia and metabolic acidosis suggests renal tubular hyperkalemia or a corticosteroid disorder.
- Hyponatremia with proteinuria and hypoalbuminuria occurs in nephrotic syndrome.

2. What is the emergency treatment of symptomatic hyponatremia?

Patients with central nervous system symptoms, particularly seizures, should receive an initial urgent IV infusion of **hypertonic saline (3%)** at a dose of 3 mL/kg. This should raise the serum sodium concentration by approximately 3 to 4 mEq/L. The dose can be repeated every 10 to 20 minutes. Increasing the serum sodium concentration by only 4 to 6 mEq/L is usually sufficient to stop hyponatremic seizures.

Brenkert TE, Estrada CM, McMorrow SP, et al. Intravenous hypertonic saline use in the pediatric emergency department. *Pediatr Emerg Care.* 2013;29(1):71–73.

KEY POINTS: HYPONATREMIA

- Hyponatremia may reflect *appropriate* antidiuretic hormone (ADH) stimulation, as in cardiac decompensation and a nonsteady state with arterial underfilling.
- Hyponatremia may reflect *inappropriate* ADH stimulation with euvolemia, as in pneumonia, brain tumor, or severe pain.
- In critically ill children who are postoperative, administration of hypotonic maintenance fluids increases the risk for hyponatremia compared with administration of isotonic fluids.
- Isotonic fluids (normal saline) administered as maintenance should be avoided in children with end-stage renal disease (ESRD), congestive heart failure, or hypertension (HTN).

3. How is the cause of hypernatremia established?

Hypernatremia is either due to **excess salt administration** or **excess free water loss**. A combination of history, clinical assessment of the patient's volume status, and measurement of the urine sodium concentration is required to establish the diagnosis.

- If the patient is **hypovolemic** and urine sodium concentration is $<$20 mEq/L, consider extrarenal water losses—diarrhea, excessive perspiration.
- If the urinary sodium concentration is $>$20 mEq/L, consider renal losses—renal dysplasia, obstructive uropathy, and osmotic diuresis.
- If the patient is **euvolemic** and the urine sodium concentration is variable, consider extrarenal losses (insensible: dermal, respiratory) and renal losses (central diabetes insipidus, nephrogenic diabetes insipidus).
- If the patient is **hypervolemic** and the urine serum concentration is (usually) $>$20 mEq/L, consider improperly mixed formula in tube feeding, excess sodium bicarbonate administration, excess salt administration, salt poisoning, and primary hyperaldosteronism (rare in children).

Muhsin SA, Mount DB. Diagnosis and treatment of hypernatremia. *Best Pract Res Clin Endocrinol Metab.* 2016;30(2):189–203.
Avner ED. Clinical disorders of water metabolism: hyponatremia and hypernatremia. *Pediatr Ann.* 1995;24(1):23–30.

4. Why can correcting hypernatremia too rapidly cause seizures?

Children with severe hyponatremia may seize before treatment is started, whereas those with hypernatremia may develop seizures in response to therapy. In patients with hypernatremic dehydration, increased extracellular osmolality draws fluid from the intracellular compartment, and cells, especially brain cells, shrink in size. However, the brain can generate idiogenic osmoles to minimize the loss of fluids. Idiogenic osmoles are principally amino acids and other organic solutes that allow brain cells to minimize cellular water loss. In fact, in chronic hypernatremia, brain size is almost normal. However, it takes about 24 hours to begin to generate or dissipate these idiogenic osmoles. Therefore, if correction of chronic hypernatremia ($>$24 hours) is too rapid, water moves from the extracellular compartment back into the cerebral intracellular compartment, thereby causing cerebral edema. This can lead to seizures, cerebral hemorrhage, and even death. To prevent this in patients with chronic hypernatremia, the serum sodium concentration should not be allowed to decrease faster than 0.5 mEq/L per hour and ideally not more than 10 to 12 mEq/L per 24 hours.

Powers KS. Dehydration: isonatremic, hyponatremic, and hypernatremic recognition and management. *Pediatr Rev.* 2015;36(7):274–283.
Schwaderer AL, Schwartz GJ. Treating hypernatremic dehydration. *Pediatr Rev.* 2005;28:148–150.

5. What is the differential diagnosis of nephrogenic diabetes insipidus (NDI)?

- *Inherited NDI* may be due to a mutation in the arginine vasopressin (AVP) receptor gene (*AVPR2*, X-linked: 90%) or aquaporin gene (*AQP2,* recessive: 10%).
- *Acquired NDI* may be due to electrolyte disturbances (hypokalemia, hypocalcemia), medications (diuretics, lithium, cisplatin), chronic kidney diseases, and tubulointerstitial disease.
- NDI can occur in renal Fanconi syndrome, renal tubular acidosis, and Bartter syndrome because of hypokalemia.

6. An infant boy presents with severe dehydration, polyuria, and hypernatremia. What is the first renal diagnosis that should come to mind?

Congenital NDI, which is caused by mutations in the vasopressin or aquaporin genes (*AVPR2* or *AQP2*), is the first renal diagnosis that should come to mind. The *AVPR2* responds to AVP to control *AQP2* expression on the tubular lumen. Aquaporins are membrane proteins involved in water transport. The genetic defect results in insensitivity in the distal nephron to AVP (ADH), so there is abnormal water reabsorption in the collecting ducts. This urine-concentrating defect is present from birth, and symptoms of irritability, poor feeding, and poor weight gain begin in the first weeks of life. High fevers, dehydration and seizures, mental retardation, and psychological problems can occur. Persistent polyuria can cause megacystis, trabeculated bladder, hydroureter, and hydronephrosis. End-stage kidney disease has been described in adults.

Bockenhauer D, Bichet DG. Nephrogenic diabetes insipidus. *Curr Opin Pediatr.* 2017;29(2):199–205.

7. What are the clinical and physiologic consequences of progressive hypokalemia (low potassium)?

- Muscle weakness and paralysis, which can lead to hypoventilation and apnea
- Constipation and ileus
- Increased susceptibility for ventricular ectopic rhythms and fibrillation, especially in children receiving digitalis
- Interference with the ability of the kidney to concentrate urine, leading to polyuria

8. What are the causes of hypokalemia?

- Diuretics, occasionally laxatives
- Metabolic alkalosis, especially in patients with pyloric stenosis
- Severe diabetic ketoacidosis with dehydration
- Diarrhea
- Renal tubular acidosis types I and II
- Renal Fanconi syndrome
- Bartter and Gitelman syndromes
- Hypermineralocorticoid states: primary hyperaldosteronism, Cushing syndrome, adrenal tumors, rare forms of congenital adrenal hyperplasia, dexamethasone-suppressible HTN
- Pituitary tumors producing adrenocorticotropic hormone
- Hyperreninemic states such as renal artery stenosis

Zeig J, Gonsorcikova L, Landau D. Current views on the diagnosis and management of hypokalaemia in children. *Acta Paediatr.* 2016;105(7):762–772.

9. Which foods are high in potassium?

Raisins, dates, avocado, beans, squash, tomatoes, lentils, baked potatoes, cocoa, oranges, bananas, French fries (especially supersized!), chocolate, and carrots are high in potassium.

10. What are the causes of hyperkalemia in children?

- **Increased potassium intake:** Increased oral intake alone does not lead to hyperkalemia as long as the ability to excrete potassium is maintained. Increased intake of potassium is an important cause of hyperkalemia when renal excretion is compromised in renal failure with oliguria-anuria or in patients taking angiotensin-converting enzyme (ACE) inhibitors. Rarely, an extremely high intake of potassium can lead to hyperkalemia (e.g., IV potassium, oral potassium penicillin, and blood transfusion using blood that has been stored a long time).
- **Decreased renal excretion:** Impaired renal function leads to reduced potassium excretion, usually in patients with oliguric/anuric acute renal failure. Initially, potassium balance is maintained by increased excretion through the functioning nephrons, until the glomerular filtration rate (GFR) decreases to <15 mL/min per 1.73 m^2.
- **Redistribution of potassium** from the intracellular to extracellular compartment. *Metabolic acidosis* results in the movement of hydrogen ions into the intracellular space to buffer the intravascular pH. To maintain electroneutrality, potassium moves out of the cell, resulting in hyperkalemia. Insulin promotes movement of potassium into cells. Therefore insulin deficiency in diabetic ketoacidosis can lead to hyperkalemia. Intravascular hyperosmolality causes water movement out of cells, dragging potassium with it (solvent drag), followed by an increase in intracellular potassium concentration, creating a favorable gradient for potassium movement out of cells.
- **Tissue breakdown** can release potassium from the cells into the extracellular fluid. This occurs with trauma, perinatal asphyxia, rhabdomyolysis, chemotherapy (causing tumor lysis syndrome), massive hemolysis (e.g., transfusion reaction), strenuous exercise, and hyperkalemic periodic paralysis.
- **Medication-induced hyperkalemia:** β-blockers, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), digoxin, succinylcholine, arginine, nonsteroidal anti-inflammatory drugs (NSAIDs), and calcineurin inhibitors may induce hyperkalemia.
- **Pseudohyperkalemia** is defined as a rise in the serum potassium concentration with a concurrently normal plasma potassium concentration. The destruction of erythrocytes after venipuncture or capillary sampling is the most frequent reason for a raised serum potassium result in children. Pseudohyperkalemia is also seen with severe thrombocytosis due to release of potassium from platelet granules, severe polycythemia, or leukocytosis. In these instances, checking a *plasma* (compared with a *serum*) potassium concentration will provide reassurance that the plasma concentration is normal.
- **Aldosterone deficiency or resistance (pseudohypoaldosteronism)** reduces potassium and hydrogen excretion and results in hyperkalemia and metabolic acidosis. Lack of aldosterone production occurs in primary adrenal insufficiency or with inborn errors of adrenal steroid metabolism (e.g., congenital adrenal hyperplasia, aldosterone synthase deficiency). Children with pseudohypoaldosteronism exhibit elevated aldosterone levels. Pseudohypoaldosteronism can occur with or without salt wasting.

Daly K, Farrington E. Hypokalemia and hyperkalemia in infants and children: pathophysiology and treatment. *J Pediatr Health Care.* 2013;27(6):486–496.

Masilamani K, van der Voort J. The management of acute hyperkalaemia in neonates and children. *Arch Dis Child.* 2012;97(4):376–380.

Lehnhardt A, Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. *Pediatr Nephrol.* 2011;26(3):377–384.

11. When are calcium infusions indicated in a patient with elevated serum potassium?

If the **serum potassium level is >8 mEq/L** or there is a **cardiac dysrhythmia**, calcium infusions are indicated. A calcium infusion is the most rapid way to treat a dysrhythmia associated with hyperkalemia, but it does not reduce serum potassium concentrations. Hyperkalemia increases the cell's membrane potential, thereby making cells more dysrhythmogenic. Hypercalcemia increases the cell's threshold potential, restores the voltage difference between these two potentials, and decreases the likelihood of a dysrhythmia. The effect of a calcium infusion is transient.

12. What are key aspects in the treatment of hyperkalemia?

- **Stabilize membrane potentials:** Ten percent calcium gluconate is used, most typically when immediate action is required to improve an abnormal electrocardiogram (ECG).
- **Promote potassium transport into cells:** Therapies include glucose + insulin and sodium bicarbonate (in the setting of acidosis—controversial in neonates). The use of beta-2 agonists (both IV and inhaled [albuterol]) can also be used.
- **Enhanced excretion of potassium:** This can be accomplished by a cation exchange resin (e.g., sodium polystyrene sulfonate—contraindicated in neonates); loop diuretic (not evidence based); and, as the ultimate therapies, dialysis or exchange transfusion in neonates.

13. What are the causes of periodic paralysis syndromes associated with both high and low potassium levels?

Inherited channelopathies are disorders produced by abnormal ion channel function. In hypokalemic periodic paralysis, about 70% of patients have a mutation in a calcium channel gene. Hypokalemic periodic paralysis may also be a manifestation of thyrotoxicosis. In hyperkalemic periodic paralysis, most cases are caused by mutations in the sodium channel SCN4A. Both diseases are characterized by intermittent weakness, usually in the morning. Of note, hyperkalemic period paralysis is a well-described and common malady in quarter horses, where it is called "Impressive syndrome" after the mutational source was found to have originated in a stallion named Impressive.

Phillips L, Trivedi JR. Skeletal muscle channelopathies. *Neurotherapeutics.* 2018;15(4):954–965.

Matthews E, Silwal A, Sude R, et al. Skeletal muscle channelopathies: rare disorders with common pediatric symptoms. *J Pediatr.* 2017;188:181–185.e6.

14. What is the undetermined serum anion gap?

The *undetermined serum anion gap* is the difference between the serum sodium concentration and the sum of chloride plus bicarbonate. The anion gap represents anions that are not normally measured, such as sulfate, organic anions, and charged albumin. The normal value is <15 mEq/L.

15. How is the serum anion gap helpful in the evaluation of metabolic acidosis?

In the presence of metabolic acidosis, the calculation of the anion gap determines which of two diagnostic pathways is more likely. If the anion gap is ***increased***, consider a cause listed under *MUDPILES* (see question 16). If the anion gap is ***normal***, consider diarrhea or renal tubular acidosis. Of note, always suspect an undetermined anion gap acidosis if the serum chloride and bicarbonate are both low.

16. What are the causes of an elevated serum anion gap acidosis?

An increased anion gap reflects the addition of an acid with its anion that is not normally measured, such as salicylate but not hydrochloric acid. The mnemonic **MUDPILES** helps with remembering the causes of an elevated anion gap:

- **M**ethanol (formic acid and formate)
- **U**remia (guanidinosuccinic acid, phosphates, sulfates, and other acids)
- **D**iabetic ketoacidosis (lactic acid, β-hydroxybutyrate, and acetoacetate)
- **P**araldehyde, **P**henformin
- **I**ron, **I**soniazid, **I**nborn errors of metabolism
- **L**actic acidosis secondary to hypoxia, severe cardiorespiratory depression, shock, prolonged seizures, or mitochondrial diseases
- **E**thanol, **E**thylene glycol
- **S**alicylate

17. How limited is the respiratory response to metabolic alkalosis?

Metabolic alkalosis occurs when a net gain of alkali or loss of acid leads to a rise in the serum bicarbonate concentration and pH. In metabolic alkalosis (as in metabolic acidosis), there is a measure of respiratory compensation in response to the change in pH. This response, which is accomplished by alveolar hypoventilation, is limited by the overriding need to maintain an adequate blood oxygen concentration. Usually the P_{CO_2} will not increase >50 to 55 mm Hg despite severe alkalosis.

18. What is the differential diagnosis in a child presenting with symptoms of primary metabolic alkalosis?

Metabolic alkalosis can be divided into two major categories on the basis of the *urinary chloride concentration* and the *response to volume expansion with a saline infusion*.

- **Saline-responsive metabolic alkalosis:** The urine chloride concentration is $<$10 mEq/L and there is significant volume depletion. Intravenously administered normal saline usually corrects the metabolic alkalosis; the classic example is pyloric stenosis.

  Causes include pyloric stenosis, profuse vomiting, excessive upper gastrointestinal suctioning, congenital chloride diarrhea, laxative abuse, diuretic use or abuse, cystic fibrosis, chloride-deficient infant formulas, posthypercapnia syndrome, and administration of a poorly reabsorbable anion (e.g., phosphate). This can also occur after treatment of organic acidemias. Treatment of diabetic ketoacidosis with insulin leads to metabolism of acetoacetate, which results in the generation of bicarbonate.
- **Saline-resistant alkalosis:** The urine chloride is high and the patient is normotensive or hypertensive. Administration of normal saline aggravates the metabolic alkalosis. In most of these cases, mineralocorticoid excess plays the central role in the generation of the alkalosis.

  Causes include hyperreninemic HTN (renal artery stenosis, renin-secreting tumor), corticosteroid treatment, severe potassium deficiency, genetic block in steroid hormone synthesis (17α-OH deficiency, 11β-OH deficiency), Liddle syndrome, Bartter syndrome, Gitelman syndrome, primary hyperaldosteronism (extremely rare in children), and licorice-containing glycyrrhizic acid.

19. Why is the urine pH often acidic (pH 5.0 to 5.5) in a child with metabolic alkalosis from severe vomiting?

Prolonged vomiting, such as is seen in pyloric stenosis, results in metabolic alkalosis because of loss of hydrogen ions and volume depletion (dehydration). There is also significant sodium, potassium, and chloride loss with a resultant hypokalemic, hypochloremic metabolic alkalosis. The volume depletion activates the renin–angiotensin–aldosterone response, which results in increased distal reabsorption of sodium and water. To retain sodium, the kidney must release other cations (hydrogen in particular) into the urine. The hydrogen ions lower the urine pH. When volume is repleted, there will be suppression of aldosterone, the urine pH will become alkaline (pH 6.5 or more), and the metabolic alkalosis will lessen. The change of the urine pH from acidotic to alkalotic is one sign of adequate volume replenishment.

This scenario is sometimes referred to as the *"paradoxical aciduria of metabolic alkalosis,"* and your attending may use the term as well. If you are feeling courageous, you could (gently) respond that it is not paradoxical at all once you understand the pathophysiology.

20. What are the symptoms and signs of hypocalcemia?

The symptoms and signs of hypocalcemia can include weakness, perioral numbness, paresthesias, carpopedal spasms, tetany, altered mental status, seizures, and a prolonged QT interval on ECG. *Chvostek sign* (tapping the parotid gland over the facial nerve in front of the ear causes facial muscle spasm with movement of the upper lip) and *Trousseau sign* (mild hypoxia induced by inflating a blood pressure [BP] cuff at pressures greater than systolic for 2 to 5 minutes, resulting in carpopedal spasm) are classically felt to be more likely in patients with hypocalcemia, but the clinical reliability of these signs, particularly Chvostek, has been called into question. They are not of value in neonates.

Hujoel IA. The association between serum calcium levels and Chvostek sign: a population-based study. *Neurol Clin Pract.* 2016;6(4):321–328.
Méneret A, Guey S, Degos B. Chvostek sign, frequently found in healthy subjects, is not a useful clinical sign. *Neurology.* 2013;80(11):1067.

21. Why should albumin be assessed in the setting of possible serum calcium abnormalities?

About one-half of calcium in the bloodstream is bound to protein (principally albumin). Thus high or low levels of protein can affect total calcium results, which may not be representative of the free (i.e., ionized) serum calcium concentration. Free calcium is the more important physiologic parameter. For every 1 g/dL below 4.0 g/dL in measured albumin, 0.8 mg/dL should be added to total serum calcium. This correction factor could change the total calcium value from the hypocalcemic to normal range. The reliability of this albumin-adjusted total calcium relationship has been questioned. When there is concern whether the total calcium measurement (corrected or uncorrected) reflects the calcium status of the patient, free (ionized) calcium should be measured, as this is biologically active form that is readily available to cells is a more accurate reflection of the physiologic calcium state.

Lian IA, Asberg A. Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. *BMJ Open.* 2018;8:e017703.

22. What rhyming words describe the potential presentations of hypercalcemia?

Bones (pain in the presence of osteolytic lesions), **Stones** (urolithiasis, HTN, polyuria), **Moans** (altered mental status), and **Groans** (nausea/vomiting, constipation, weakness).

23. Describe the stepwise approach to treating a child with symptomatic hypercalcemia

- IV fluids with normal saline to increase excretion into urine
- If signs of heart failure or renal failure, consider use of a loop diuretic
- Calcitonin or bisphosphonates (to inhibit bone resorption, if present)
- Cinacalcet (Sensipar, a calcimimetic) is an allosteric activator of calcium-sensing receptors → causes a decrease in parathyroid hormone (PTH) release
- Glucocorticoids (to decrease intestinal absorption)

Davies JH. Approach to the child with hypercalcemia. *Endocr Dev.* 2009;16:83–114.

24. In what clinical settings should hypophosphatemia be suspected?

Hypophosphatemia can present with a wide variety of symptoms, including muscle weakness and mental status changes. Hypophosphatemia can develop from the redistribution of phosphate from the extracellular space into cells. This can occur with refeeding syndrome due to the effects of glycolysis, insulin, and glucagon (which promote the extracellular ➔ intracellular transfer) when a severely malnourished child is renourished and after parathyroidectomy in so-called "hungry bone syndrome" with postsurgical influxes of calcium and phosphate into bone. Gastrointestinal causes of hypophosphatemia include reduced intake, increased loss (chronic diarrhea), and interference with absorption (aluminum/magnesium antacids). Phosphate is also lost through the kidneys with hyperparathyroidism, vitamin D deficiency or resistance, primary renal phosphate wasting, and renal Fanconi syndrome.

ACUTE KIDNEY INJURY

25. Why has the term *acute kidney injury* (AKI) replaced *acute renal failure*?

AKI reflects more appropriately the concept that smaller reductions in kidney function (short of complete organ failure) have significant clinical repercussions in terms of morbidity and mortality.

26. What clinical and laboratory observations are useful for distinguishing prerenal oliguria (decreased effective circulating volume) from the oliguria of intrinsic AKI?

Clinical assessment of hydration, volume, and perfusion status is critical because these are more likely to be impaired in a prerenal state. In patients with intrinsic AKI, the volume status is more likely to be normal or increased; there may be evidence of edema or vascular congestion. If the assessment of the volume status suggests a volume deficit, a fluid bolus with normal saline can be both diagnostic and therapeutic. Laboratory studies that assist are summarized in Table 12.1.

Table 12.1 Laboratory Studies That May Distinguish Prerenal Oliguria From Acute Tubular Necrosis

PARAMETER	PRERENAL OLIGURIA	RENAL OLIGURIA
Random U_{Na} (mEq/L)	<20	>40
FE_{Na}*	$<1\%$	$>1\%$
Urine osmolality (mOsm/L)	>500	<300

$FE_{Na} = ([U_{Na} \times P_{Creat}] / [P_{Na} \times U_{Creat}]) \times 100\%$ (on a randomly collected, spot urine).

27. What is the most common cause of AKI in young children in the United States?

This used to be hemolytic uremic syndrome (HUS), which in most cases is caused by gastrointestinal infection with Shiga toxin–producing *Escherichia coli*, especially the O157:H7 serotype. However, cases of **acute tubular necrosis** in infancy and childhood from *hypoxic*, *hypotensive*, and/or *hypovolemic insults* or *drug-induced injury* now represent the largest group of causes. New biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL, associated with renal ischemia), predict the development of AKI before estimated glomerular filtration rate (eGFR) based on creatinine level decreases. The severity and duration of AKI are important predictors of chronic kidney disease and long-term mortality.

The causes of AKI are listed in Table 12.2.

Bennett MR, Nehus E, Haffner C, et al. Pediatric reference ranges for acute kidney injury biomarkers. *Pediatr Nephrol.* 2015; 30(4):677–685.

Siew ED, Furth SL. Acute kidney injury: a not-so-silent disease. *Kidney Int.* 2014;85:494–495.

Table 12.2 Causes of Acute Kidney Injury (AKI)

Prerenal Causes of AKI	
Volume depletion	Severe diarrhea Protracted vomiting Osmotic diuresis Diuretics Extensive burns Hemorrhage
Decreased effective blood volume	Septic shock Anaphylaxis Nephrotic syndrome
Cardiac failure	Anatomical malformation Arrhythmias Cardiomyopathy Tamponade Postcardiac surgery
Intrinsic Causes of AKI	Postinfectious glomerulonephritis Lupus nephritis Henoch-Schönlein purpura nephritis IgA nephropathy Crescentic glomerulonephritis
Vascular	Renal venous thrombosis Vasculitis Nonsteroidal anti-inflammatory agents ACE inhibitors Hemolytic uremic syndrome
Tubular (ATN)	Severe prerenal failure Asphyxia/hypoxemia Crystal obstruction Medications Toxins Tumor-lysis syndrome
Interstitial nephritis	Allergic interstitial nephritis TINU syndrome Malignancy infiltrate Pyelonephritis Sarcoidosis
Postrenal Causes of AKI	Bilateral nephrolithiasis Neoplasm

ACE, Angiotensin-converting enzyme; *ATN*, acute tubular necrosis; *IgA*, immunoglobulin A; *TINU*, tubulointerstitial nephritis and uveitis.

28. What is the triad of clinical findings of HUS?

- **Acute renal failure** with oliguria, anuria, and, rarely, polyuria
- **Acute hemolytic anemia**: microangiopathic with fragmented red blood cells (RBCs) or schistocytes, nonimmune, Coombs negative
- **Thrombocytopenia**

Kaplan BS, Drummond KN. The hemolytic-uremic syndrome is a syndrome. *N Engl J Med.* 1978;298(17):964–966.

29. What is the most frequent cause of HUS?

Shiga toxin–producing *E. coli* OH157:H7 is the most frequent cause of HUS in the United States. Shiga toxin–producing *E. coli* 0104:H4 infection caused a severe epidemic of HUS in Europe in 2011. Endothelial cell injury with secondary glomerular capillary microthrombi is central to the pathogenesis of HUS caused by Shiga toxin–producing *E. coli.* This is the most frequent cause of HUS, but there are other known causes of which atypical hemolytic uremic syndrome (aHUS) comprises about 10% of all causes. Genetic mutations increase the risk for aHUS and may lead to uncontrolled activation of the complement system when it is triggered.

Rodríguez de Córdoba S, Hidalgo MS, Pinto S, Tortajada A. Genetics of atypical hemolytic uremic syndrome (aHUS). *Semin Thromb Hemost.* 2014;40(4):422–430.

30. Does the use of antibiotic therapy in children with diarrhea caused by *E. coli* OH157:H7 prevent HUS?

This is controversial. A study showed that children who received antibiotics (usually sulfa-containing or β-lactam antibiotics) during outbreaks had a higher rate (50% versus 7%) of HUS. Subsequent meta-analyses have shown no protection and no association. Most specialists opt not to treat patients with *E. coli* OH157:H7 gastroenteritis with antibiotics because no benefit has been proven.

Thomas DE, Elliott EJ. Interventions for preventing diarrhea-associated hemolytic uremic syndrome: systematic review. *BMC Public Health.* 2013;13:799.

Safdar N, Said A, Gangnon RE, et al. Risk of hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* 0157:H7 enteritis: a meta-analysis. *JAMA.* 2002;288:996–1001.

31. Can anything be done to lessen the severity of renal disease in children with HUS caused by *E. coli* OH157:H7?

About 15% of patients with *E. coli* 0157:H7 gastroenteritis develop HUS within 2 to 14 days of onset of diarrhea. IV volume expansion before the onset of HUS, if indicated, may decrease the frequency of oliguric or anuric renal failure in patients with *E. coli* OH157:H7 at risk for HUS. Additional therapies, such as plasma exchange, immunoadsorption, Shiga toxin–binding agents, and complement inhibitors (e.g., eculizumab), are currently under study.

Fakhouri F, Zuber J, Frémeaux-Bacchi V, Loirat C. Haemolytic uraemic syndrome. *Lancet.* 2017;390:681–696.

Keir LS, Marks SD, Kim JJ. Shigatoxin-associated hemolytic-uremic syndrome: current molecular mechanisms and future therapies. *Drug Des Devel Ther.* 2012;6:195–208.

Hickey CA, Beattie TJ, Cowieson J, et al. Early volume expansion during diarrhea and relative nephroprotection during subsequent hemolytic uremic syndrome. *Arch Pediatr Adolesc Med.* 2011;165:884–889.

32. Why is Shiga toxin–associated HUS so terrifying for patients, family, and physicians?

Shiga toxin–associated HUS is terrifying because patients can die, intensive care is required for about 50% of cases, serious extrarenal complications can develop, and patients who recover may have chronic sequelae. Fortunately, about 70% of patients recover completely from the acute episode. The acute death rate is now <4%, and serious long-term complications are <15%. The kidneys bear the brunt of the long-term damage, which includes proteinuria (15% to 30% of cases), HTN (5% to 15%), chronic kidney disease (CKD, 9% to 18%), and ESRD (3%). A smaller number have extrarenal sequelae, including colonic strictures, cholelithiasis, diabetes mellitus, or brain injury. Most of the patients who progress to ESRD do not recover normal renal function after the acute episode. The most important risk factors for both poor acute and long-term renal outcome are anuria for >10 days and prolonged need for dialysis >3 weeks. After the acute episode, all patients must be followed for at least 5 years, and patients should be followed indefinitely if there is proteinuria, HTN, or a reduced eGFR.

Spinale JM, Ruebner RL, Copelovitch L, Kaplan BS. Long-term outcomes of Shiga toxin hemolytic uremic syndrome. *Pediatr Nephrol.* 2013;28:2097–2105.

33. What is meant by aHUS?

This term describes a group of patients of all ages who present with the classic features of HUS but who **do not have Shiga-like–toxin producing *E. coli* (STEC)** as the cause. Atypical HUS accounts for about 5% to 10% of HUS cases. Several genetic mutations have been identified that appear to cause excessive activation of the complement system. The classic distinctions between so-called typical and atypical HUS are starting to blur with new discoveries in abnormalities in genes that regulate the alternative pathway (AP) of complement. Many cases of aHUS may even have antecedent diarrhea. Compared with classic HUS, the prognosis for aHUS is worse. Fifty percent may progress to ESRD compared with 85% of cases of typical HUS who recover renal function. The use of eculizumab, a specific anti-C5 monoclonal antibody that blocks alternative complement pathway activation, has dramatically improved the outcome of aHUS patients with known or suspected mutations in complement regulatory genes.

Jokiranta TS. HUS and atypical HUS. *Blood.* 2017;129(21):2847–2856.

Kaplan BS, Ruebner RL, Spinale JM, Copelovitch L. Current treatment of atypical hemolytic uremic syndrome. *Intractable Rare Dis Res.* 2014;3(2):34–45.

Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med.* 2013;368(23):2169–2181.

34. What are indications for dialysis in AKI?

A helpful mnemonic is **AEIOU: A**cidemia, **E**lectrolyte abnormalities, **I**ncreased BP, **O**verload (volume), and **U**remia.

- Severe metabolic acidemia that cannot be controlled with sodium bicarbonate
- Elevated blood urea nitrogen (BUN) and creatinine concentrations in the context of anuria or uncontrolled metabolic abnormalities. There are no established critical levels of BUN or creatinine above which dialysis needs to be instituted. However, when the creatinine reaches 10 mg/dL or the BUN is $\geq$100 mg/dL, the GFR is usually markedly reduced, and this results in one or more of the following abnormalities:
  - Hyperkalemia that is either rapidly rising or stable at a dangerously high level, especially with ECG changes, that cannot be controlled by standard treatments; other severe electrolyte disturbances, including symptomatic hyponatremia, hypocalcemia, hyperphosphatemia, and hyperuricemia
  - Volume-dependent HTN or signs of congestive heart failure (CHF) not responsive to diuretic treatment
  - Urgent need for a blood transfusion in the presence of fluid overload and/or HTN
  - Acute signs or symptoms of encephalopathy

CHRONIC KIDNEY DISEASE

35. Based on GFR estimations and serum creatinine levels, how are AKI and CKD defined?

- *Criteria for AKI*: GFR $<$60 mL/min per 1.73 m^2 for $<$3 months *or* a decrease in GFR by $>$35% or increase in serum creatinine (SCr) by $>$50% for $<$3 months
- *Criteria for CKD:* Presence of AKI criteria for $>$3 months

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Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol.* 2015;10(4):554–561.

36. What are the stages of CKD?

There are five stages of CKD (Table 12.3). The stages are based on GFR.

Table 12.3 Stages of Chronic Kidney Disease

STAGE	GFR*	DESCRIPTION	TREATMENT
1	90+	Normal kidney function but urine or imaging abnormalities	Observation, control blood pressure
2	60-89	Mildly reduced function	Observation, control blood pressure control
3A 3B	45-59 30-44	Moderately reduced function	Observation, control blood pressure and risk factors
4	15-29	Severely reduced function	Plan for end stage renal failure
5	<15 or on dialysis	End-stage kidney disease	Discuss treatment choices

[*] *GFR*, Glomerular filtration rate (min/1.73 m^2).

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* 2013;3:1-150.

37. What are the main causes of CKD in children that result in renal transplantation?

- Obstructive uropathy
- Aplastic, hypoplastic, and dysplastic kidneys
- Focal segmental glomerulosclerosis

Whyte DA, Fine RN. Chronic kidney disease in children. *Pediatr Rev.* 2008;29(10):335–340.

38. Your nephrology attending likes to use the Socratic method of teaching. “What are four major endocrine and cardiac medications that have dramatically improved the lives and outcomes of children with CKD?” is a favorite question.

- Use of **erythropoietin**, a hormone normally produced in the kidney, has largely eliminated the need for blood transfusions in children with CKD.
- Use of **1,25-dihydroxycholecalciferol**, an active form of vitamin D normally produced in the kidney, has dramatically prevented or treated osteodystrophy.

- Growth hormone (GH) is not produced by the kidney. However, **recombinant GH** administration results in growth acceleration and improved appetite in growth-retarded children with CKD.
- Inhibition of the renin–angiotensin–aldosterone system with ***ACE inhibitors* or *ARBs*** has helped control HTN and reduced the rate of glomerular fibrosis and slowed the progression to ESRD.

39. What is a newer term for renal osteodystrophy?

Renal osteodystrophy has traditionally been the term used to describe the bone and mineral pathology caused by the endocrine and electrolyte derangements in CKD. The moniker **"chronic kidney disease–mineral and bone disorder (CKD–MBD)"** was recommended by an international consensus committee in 2009 to better describe the systemic changes that take place in CKD.

40. What hormonal elevation is key in the pathogenesis of CKD–MBD?

Hyperparathyroidism is key. Decreased GFR results in retention of phosphate and hyperphosphatemia. Additionally, there is decreased renal 1,25-dihydroxyvitamin D production. These two factors lead to decreased absorption of calcium from the gastrointestinal tract and decreased responsiveness of bone to PTH, which results in hypocalcemia. The hypocalcemia leads to an increased release of PTH, which then increases bone resorption. A long-term sequela of this secondary hyperparathyroidism from CKD can be bone marrow fibrosis.

41. Why is it important to recognize CKD–MBD at an early stage?

Recognition of **osteodystrophy** (which begins when the GFR is half of the normal rate) is important because early intervention with calcitriol, vitamin D, and phosphate binders can prevent and/or heal the bone disease (but not necessarily enhance growth). Furthermore, in states of chronic acidosis, the skeleton acts as a buffer for the net acid retained. This results in the release of calcium, which contributes to further osteopenia and bone disease.

42. Why is FGF23 an important evolving concept in CKD–MBD?

Changes in calcium/phosphate metabolism in CKD are characterized by hyperphosphatemia, hypocalcemia, calcitriol deficiency, and hyperparathyroidism. A key regulator of this complex system is *FGF23,* a circulating peptide produced in the osteocyte that regulates renal phosphate excretion. PTH is still the most important biomarker, but novel biomarkers, such as FGF23, and noninvasive imaging techniques are emerging that can allow for individual classification and monitoring in the progression of CKD-MBD.

Kemper MJ, van Husen M. Renal osteodystrophy in children: pathogenesis, diagnosis and treatment. *Curr Opin Pediatr.* 2014;26:180–186.

43. What are the ciliopathies?

This is an important question because the answer opens up a whole new book in the understanding of many inherited renal conditions (Table 12.4). Diverse developmental and degenerative single-gene disorders, such as polycystic kidney disease, nephronophthisis, retinitis pigmentosa, Bardet-Biedl syndrome, Joubert syndrome, and Meckel syndrome, are categorized as ciliopathies, a recent concept that describes diseases characterized by dysfunction of a hair-like cellular organelle called the *primary cilium*. Most of the proteins that are altered in these single-gene disorders function at the level of the cilium–centrosome complex.

Braun DA, Hildebrandt F. Ciliopathies. *Cold Spring Harb Perspect Biol.* 2017;9(3):a028191.
Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. *N Engl J Med.* 2011;364:1533–1543.

Table 12.4 Single-Gene Ciliopathies

Dominant disorders	Autosomal dominant polycystic kidney disease Von Hippel-Lindau disease
Recessive disorders	Autosomal recessive polycystic kidney disease Nephronophthisis
	Bardet-Biedl syndrome
	Retinal-Renal syndromes
	Senior-Løken syndrome
	Joubert syndrome
	Meckel syndrome
	Alstrom syndrome
	Sensenbrenner syndrome

44. Nephronophthisis is difficult to pronounce and spell, but what is it?

Nephronophthisis (one of the ciliopathies) is the most frequent genetic cause of ESRD in the first 3 decades of life (median age: 13 years) and is characterized by cysts restricted to the corticomedullary junction. Kidney size is normal or small. Mutations in more than 11 recessive genes (*NPHP1* to *NPHP11*) have been identified as causes of nephronophthisis. Mutations in *NPHP1* cause juvenile nephronophthisis type 1. Clinical features of juvenile nephronophthisis include anemia, polyuria, polydipsia, isosthenuria, growth failure, and progression to ESRD.

45. Which is more common in children: autosomal dominant polycystic kidney disease (ADPKD) or autosomal recessive polycystic kidney disease (ARPKD)?

ADPKD is the more common, and it also is the most prevalent monogenic disorder in humans. It is characterized by progressive enlargement of renal cysts. Cysts are typically diagnosed incidentally (e.g., affected parent, imaging study for another reason). ADPKD may present with pain, hematuria, urinary tract infection (UTI), HTN, and calculi and can even be diagnosed in utero. There is a large interfamilial and intrafamilial variation with genetic heterogeneity and modifier genes. Two polycystic kidney (PKD) genes have been identified: *PKD1* (85% of cases) and *PKD2* (15% of cases).

46. What anatomic features characterize ADPKD?

Bilateral renal cysts are the predominant feature, but involvement of other organs can include cysts (liver, seminal vesicles, pancreas, arachnoid); intracranial aneurysms; mitral valve prolapse; diverticulosis; and, rarely, aortic root dilatation and aortic aneurysms.

47. How is ADPKD diagnosed and managed?

A **renal ultrasound** is usually adequate. DNA studies are rarely indicated. Presymptomatic diagnosis in children outweighs any benefits until effective treatments are available. It is important to counsel presymptomatic individuals before testing.

Monitor BP and urine in individuals with a family history of ADPKD. Avoid contact sports. Use of ACE inhibitors to control BP has improved outcomes. Encourage water intake to suppress ADH and retard cyst growth. The prognosis is excellent in children.

Sommerer C, Zeier M. Clinical manifestation and management of ADPKD in Western countries. *Kidney Dis (Basel).* 2016;2(3):120–127.
Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet.* 2007;369(9569):1287–1301.
Polycystic Kidney Foundation. www.PKDcure.org. Accessed March 15, 2020.

48. Why was the term *infantile polycystic kidney disease* replaced with ARPKD?

This is because some patients have been diagnosed in adulthood with moderate renal insufficiency and ESRD. The characteristic dilatation of the renal collecting ducts begins during development and can present at any stage from infancy to adulthood. Renal insufficiency often occurs in utero and may lead to early abortion or oligohydramnios and lung hypoplasia. However, there are affected neonates who have no evidence of renal dysfunction. Up to 30% of patients die in the perinatal period, and those surviving the neonatal period can reach ESRD in infancy, early childhood, or adolescence. The clinical spectrum of ARPKD includes bilateral renal enlargement with microcysts, arterial HTN, and intrahepatic biliary dysgenesis. Affected infants develop congenital hepatic fibrosis, and some have nonobstructive dilation of the intrahepatic bile ducts (Caroli disease). Cholangitis, variceal bleeding, and hypersplenism are serious complications. ARPKD is caused by mutations in the *PKDHD1* gene on chromosome 6.

Büscher R, Büscher AK, Weber S, et al. Clinical manifestations of autosomal recessive polycystic kidney disease (ARPKD): kidney-related and non-kidney-related phenotypes. *Pediatr Nephrol.* 2014;29(10):1915–1925.

ENURESIS/DYSFUNCTIONAL VOIDING

49. How common is nocturnal enuresis in older children?

At the age of 5 years, about 20% of children (boys more than girls) wet the bed at least once monthly. Nightly wetting is not as common (<5%). By the age of 7 years, the overall rate is down to 10%, and by the age of 10 years, it is down to 5%. As a general rule, after age 7 years, nocturnal enuresis resolves at a rate of 15% per year so that by age 15 years, about 1% to 2% of teenagers still have nocturnal enuresis, which can continue into adulthood.

50. Why does nighttime bed-wetting persist in some children?

Ninety-seven percent or more of the causes are nonpathologic, and a number of explanations have been theorized: **maturational delay of neurodevelopmental processes**, **small bladder capacity**, **genetic influences**, **difficulties with waking**, and **decreased nighttime secretion of ADH**. No data support the belief that wetting occurs during "deep sleep." Genetic influences are quite strong. If both parents were enuretic, a child's likelihood is about 75%; if one parent was involved, the likelihood is about 50%. Psychological problems are unlikely to cause nocturnal enuresis, but they are more common if daytime symptoms are present.

Graham KM, Levy JB. Enuresis. *Pediatr Rev.* 2009;30(5):165–172.

51. What treatments are available for nocturnal enuresis?

The therapeutic approach depends in large part on the age of the patient, the effect of the problem on the patient, and the parents' attitude. It is important to realize that 15% of patients per year will spontaneously improve.

- **Dry bed training:** Self-waking routines, cleanliness training, bladder training, and rewards for dry nights; generally not effective as a sole intervention
- **Enuresis alarms:** Portable alarms (auditory and/or vibratory) worn by the child at night and designed to awaken the child to the sensation of a full bladder; success rates as high as 70%; safe, but requires parental and child motivation
- **Desmopressin:** Synthetic analog of vasopressin that, at the renal level, increases distal tubular reabsorption of water, thus diminishing nighttime bladder volume; available in oral and nasal forms; up to 70% effective; high relapse rate after discontinuation (similar to placebo); possible adverse effects, including nasal irritation and hyponatremia; expensive
- **Imipramine:** Bladder effects include increasing capacity and decreasing detrusor excitability; high relapse rate; important central nervous system side effects in 10% (e.g., drowsiness, agitation, sleep disturbances)

52. A 7-year-old presents with problems of intermittent daytime urinary incontinence with a normal urinalysis and a negative urine culture. What evaluation is needed?

The differential diagnosis is broad with considerable clinical overlap, including problems with bladder storage (overactive bladder or urge syndrome) and dysfunctional voiding, in which the child habitually contracts the external urinary sphincter during micturition. Keys to diagnosis are a good history of the pattern and circumstances of the incontinence, urinalysis/urine culture, a bladder diary, uroflowmetry (and assessment of postvoid residual), and baseline renal ultrasonography with efforts to exclude any neurogenic, infectious, or anatomic abnormalities. The prevalence in school-age children (ages 5 to 13 years) of daytime incontinence is remarkably high, affecting 7% to 10% in various studies. The problem can have profound psychosocial effects, so attempts at a diagnosis are key. Urology referral is often required.

Nieuwhof-Leppink AJ, Schroeder RPJ, van de Putte EM, et al. Daytime urinary incontinence in children and adolescents. *Lancet Child Adolesc Health.* 2019;3(7):492–501.

Chang SJ, Van Laecke E, Bauer SB, et al. Treatment of daytime urinary incontinence: a standardization document from the International Children's Continence Society. *Neurourol Urodyn.* 2017;36(1):43–50.

53. What is the term for extraordinary daytime urinary frequency?

Pollakiuria is characterized by a very high daytime frequency of micturition (as many as 50 times per day). Symptoms are limited to the daytime. It occurs around 4 to 6 years in either gender and is associated with a history of recent death or life-threatening event in the family. It usually runs a benign, self-limiting course over 6 months. No specific treatment, apart from reassurance, is necessary. Children presenting with frequency, however, merit clinical investigation to exclude other pathologic causes.

54. Why is giggle incontinence not a laughing matter?

This uncommon form of daytime incontinence usually occurs in school-age girls. There is moderate to large amounts of urinary leakage triggered by laughing. The accepted theory is that of a central inactivation (cataplexy) in association with laughter resulting in incontinence. It is a diagnosis of exclusion and is usually established on history and is supplemented by the absence of other voiding symptoms and normal investigations. Giggle incontinence has a significant adverse effect on social life, and this is often why medical assistance is sought.

55. What is the normal bladder capacity in children?

Bladder capacity reflects voided volumes and is an important factor in the evaluation of children with voiding dysfunction. It is estimated (in milliliters) by the formula: **[30 + (age in years × 30)]**. The formula is useful up to age 12 years, after which age the estimated bladder capacity is 390 mL (an approximate adult value).

Nevéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. *J Urol.* 2006;176:314–324.

GLOMERULAR DISEASES

56. What constellation of findings is used to define nephrotic syndrome?

Nephrotic syndrome is defined by **proteinuria**, **hypoalbuminemia**, **edema**, and **hypercholesterolemia**. There are, however, patients with nephrotic-range proteinuria and mild-to-moderate hypoalbuminemia or even normal albumin levels in whom there is no hyperlipidemia or peripheral edema. A proportion of such patients have focal segmental glomerulosclerosis (FSGS).

57. What differentiates nephrotic syndrome from nephritis?

The suffix “-itis” implies evidence of glomerular inflammation. On biopsy of a child with glomerulonephritis, this is an increased number of cells within the glomerulus and/or the presence of leukocytes. Glomerular inflammation disrupts glomerular basement membrane structure and function and leads to hematuria and proteinuria. The proteinuria may be minimal to massive, depending on the type and severity of the nephritis. The finding of RBC casts (Fig.12.1) in the urine is, with rare exceptions, diagnostic of glomerulonephritis.

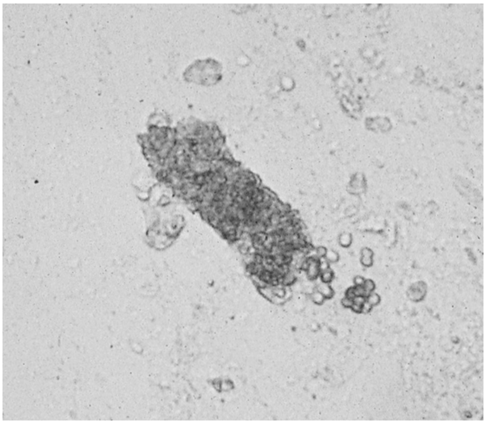

Fig. 12.1 Red blood cell cast from a patient with streptococcal glomerulonephritis. These casts are almost always associated with glomerulonephritis or vasculitis and virtually exclude extrarenal disease. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis.* 4th ed. St. Louis, MO: Mosby; 2002:458.)

Nephrosis is another term for nephrotic syndrome. There are many causes of nephrotic syndrome, and confusingly several different histopathologic changes even with the same cause. Lupus nephritis is a classic example. Not only are there several causes of lupus (e.g., genetic, drugs such as hydralazine) but also at least five classes of renal pathologic changes. Most glomerulopathies present with a nephritic or a nephrotic syndrome. Many patients present with a mixed picture of nephritic/nephrotic syndrome.

58. A 12-year-old girl complains of a sore throat and passes painless, cola-colored urine for 2 days. When you see her a few days later she has amber-colored urine, microscopic hematuria, 2+ proteinuria, RBC casts, and no other complaints or clinical findings. What is the most likely cause of this presentation?

IgA nephropathy (IgAN) is by far the most likely cause. The simultaneous occurrence of upper respiratory symptoms and gross hematuria make poststreptococcal glomerulonephritis less likely. IgAN has a more benign clinical course in children than adults; pediatric patients are more likely to have minimal histologic lesions and less likely to have advanced chronic lesions. IgAN is the most common type of primary glomerular disease worldwide. The clinical and histologic features of IgAN are variable and include microscopic hematuria, synpharyngitic hematuria (i.e., hematuria with or just after upper respiratory infection [URI]), recurrent hematuria, proteinuria, nephrotic syndrome, nephritic syndrome, and acute renal failure. Glomerular deposits of IgA characterize IgAN (Fig. 12.2). There is no proven therapy, but ACE inhibitors may retard or prevent sclerosis.

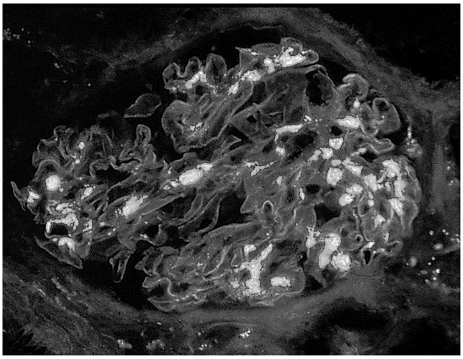

Fig. 12.2 Diffuse mesangial IgA nephropathy is seen on indirect immunofluorescence with fluorescein isothiocyanate—anti-IgA. (From Johnson RJ, Feehally J, Floege J. *Comprehensive Clinical Nephrology.* 5th ed. Philadelphia, PA: Saunders; 2015:266–277.)

59. What is the long-term prognosis for patients with IgAN?

IgAN is the most common form of glomerulonephritis that results in ESRD. Twenty percent to 25% of patients will progress to ESRD over 25 years. Risk factors for developing ESRD include elevated serum creatinine, proteinuria of $\geq$1 g per day, HTN, tubular atrophy, severity of interstitial fibrosis, and the extent of glomerular sclerosis.

Rodrigues JC, Haas M, Reich HN. IgA nephropathy. *Clin J Am Soc Nephrol.* 2017;12(4):677–686.

Haas M. IgA nephropathy in children and adults: comparison of histologic features and clinical outcomes. *Nephrol Dial Transplant.* 2008;23(8):2537–2545.

60. During the evaluation of a patient with hematuria, what features suggest acute glomerulonephritis, chronic glomerulonephritis, or nephrotic syndrome?

The three major presentations of glomerular involvement are:

- *Acute glomerulonephritis*: Edema, proteinuria of 1+ or greater, HTN, oliguria, dysmorphic RBCs, or RBC casts on urinalysis
- *Chronic glomerulonephritis*: Minimal acute symptoms; may have chronic fatigue, failure to thrive, normochromic normocytic anemia, HTN, abnormal urinalysis, high BUN and creatinine concentrations (azotemia), metabolic acidosis, hypocalcemia, and hyperphosphatemia
- *Nephrotic syndrome*: Proteinuria of $>$40 mg/m^2 per hour, edema, hypoalbuminemia, and hypercholesterolemia

61. If glomerulonephritis is suspected, what laboratory tests should be considered?

- *First-line tests:* dipstick urinalysis, urine microscopy, serum electrolytes, BUN and serum creatinine, serum C3 and C4, streptococcal serology (antistreptolysin O [ASO] titer or Streptozyme), throat culture, skin culture if impetigo is present, serum albumin
- *Second-line tests:* antinuclear antibody (ANA), anti-DNA antibodies (if lupus nephritis is suspected), hepatitis B and C serology (for patients in endemic areas, those previously transfused, or individuals who engage in high-risk behavior), antineutrophil cytoplasmic antibody (ANCA) (if rapidly progressive glomerulonephritis or vasculitis is suspected)

62. Which glomerulonephritides have a genetic basis?

See Table 12.5.

Table 12.5 Glomerular Diseases With Genetic Causes

	MUTATION	INHERITANCE
Congenital nephrotic syndrome	*NPHS1*	Recessive
Diffuse mesangial sclerosis	*WT1*	Recessive
Denys-Drash syndrome	*WT1*	Recessive
Frazier syndrome	*KTS*	Recessive
FSGS	*NPHS2, TRPC6, ACTN4, INF2,* and *PLCE1*	Recessive or dominant
Alport syndrome	*COL4A5*	X-linked Recessive, dominant
Nail–patella syndrome	*LMX1B*	Dominant
Steroid resistant NS with sensorineural deafness	*COQ6*	Dominant
C3 glomerulopathy	Factor H, *CFHR*	Recessive

FSGS, Focal segmental glomerulosclerosis.

Hildebrandt F. Genetic kidney diseases. *Lancet.* 2010;375:1287–1295; Carney EF. Glomerular disease: frequency of podocyte-related gene mutations in FSGS. *Nat Rev Nephrol.* 2014;10:184.

63. Which types of glomerulonephritis are associated with hypocomplementemia?

- **Postinfectious glomerulonephritis**, including poststreptococcal (acute poststreptococcal glomerulonephritis [ASPGN]); staphylococcus in subacute bacterial endocarditis
- **Lupus nephritis**
- **Immune complex membranoproliferative glomerulonephritis**
- **C3 glomerulopathy**
- **aHUS**

64. Does the treatment of streptococcal skin or pharyngeal infections prevent ASPGN?

No. Treatment of impetigo or pharyngitis does not prevent glomerulonephritis in the index case. However, treatment lessens the likelihood of contagious spread to children who may be susceptible.

65. What is the usual time course for ASPGN?

Symptoms and signs begin about **7 to 14 days after pharyngitis** and **as long as 6 weeks after a pyoderma** with Lancefield group A β-hemolytic streptococci. Children typically have tea-colored urine and edema. The acute phase (HTN, gross hematuria, oliguria) can last as long as 3 weeks. Serum C3 levels may remain depressed for up to 8 weeks, but persistence beyond this point suggests another diagnosis. Chronic microscopic hematuria can persist for up to 2 years. In pediatric patients, full recovery is expected, and progression to chronic renal insufficiency is rare.

66. What percentage of children with ASPGN have elevated levels of serum ASO titers?

About **80% to 85%** of children with documented pharyngeal streptococcal infections develop elevated ASO titers. Streptolysin O is bound to lipids in the skin, so that the percentage of individuals with streptococcal impetigo who develop positive ASO titers is much lower. For this reason, a normal ASO titer does not rule out recent streptococcal infection. Screening for other streptococcus-associated antigens, antihyaluronidase, and anti-DNAase B titers will be positive in $>$95% of children with documented streptococcal infection.

67. If pharyngitis and the brown urine occur on the same day or within 1 or 2 days, does this make ASPGN less likely?

Yes. The occurrence of upper respiratory symptoms and gross hematuria at the same time (synpharyngitic) is more characteristic of IgAN. Serum C3 is normal in IgAN. These children may have recurrent episodes of synpharyngitic (i.e., at the time of or shortly after a URI) gross hematuria.

68. A 7-year-old girl has a typical presentation of poststreptococcal glomerulonephritis with positive ASO titers and low serum C3, but over the next 3 months she has recurrent episodes of gross hematuria and her C3 remains very low. What diagnosis should be considered?

Recurrent gross hematuria and persistently low C3 are extremely rare in ASPGN. **C3 glomerulopathy** is a recently characterized disease that includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). Evaluation includes testing for alternative complement regulatory genes, presence of C3 nephritic factor (C3NeF), and a kidney biopsy. The histologic feature is glomerular deposits of C3 or dense deposits in the glomerular basement membrane. Genetic abnormalities occur in the complement AP. The serum C3 level is often low, but the C4 level is normal. Acquired AP dysregulation in DDD and C3GN may be induced by C3NeF, which is found in 80% of patients with DDD and 45% with C3GN. C3GN may lead to ESRD within 10 years of the diagnosis in 36% to 50% of patients. Recurrences may occur after renal transplantation. Inhibition of complement C3 or C5 is a promising treatment option.

Prasto J, Kaplan BS, Russo P, et al. Streptococcal infection as possible trigger for dense deposit disease (C3 glomerulopathy). *Eur J Pediatr.* 2014;173:767–772.

Servais A, Noël LH, Frémeaux-Bacchi V, et al. C3 glomerulopathy. *Contrib Nephrol.* 2013;181:185–193.

69. You are on rounds, and a know-it-all nephrology fellow asks you, “What are the renal complications of HIV infection?”

The short answer is “**any and every renal syndrome or condition**.” HIV nephropathy can result from direct kidney infection with HIV or from the adverse effects of antiretroviral drugs. Patients with HIV disease are also at risk for developing prerenal azotemia due to volume depletion as a result of salt wasting, poor nutrition, nausea, or vomiting.

When faced with a known clinical problem with an unexpected complication, ask yourself three questions:

- Is the complication related to the disease itself?
- Is it related to the treatment of the disease?
- Is it unrelated to either?

This approach led to the observation that tenofovir was the cause of rickets and renal Fanconi syndrome in a boy with congenital HIV infection. The advent of the newer antiretroviral drugs has significantly reduced the incidence of HIV-related nephropathy.

Wood SM, Shah SS, Steenhoff AP, et al. Tenofovir-associated nephrotoxicity in two HIV-infected adolescent males. *AIDS Patient Care STDS.* 2009;23:1–4.

HEMATURIA

70. How common is hematuria in children?

Microscopic hematuria ($>$5 RBCs/high-power field [HPF]) is relatively common (**0.5% to 2% of school-age children**) and often transient. In 70% to 80% of cases, no etiology is identified.

71. What is the most identifiable cause of microscopic hematuria?

Hypercalciuria, defined as elevated urinary calcium excretion without concomitant hypercalcemia. In areas of the southeastern United States, often called “the stone belt,” this is a common cause of isolated hematuria; nearly one-third of children with microscopic hematuria have hypercalciuria as the cause. It is less common in other parts of the United States. Overall, 3% to 6% of children have idiopathic hypercalciuria.

Srivastava T, Schwaderer A. Diagnosis and management of hypercalciuria in children. *Curr Opin Pediatr.* 2009;21:214–219.

72. What distinguishes lower from upper tract bleeding?

As a general rule, brown, tea-colored, or cola-colored urine suggests *upper tract bleeding,* whereas bright red blood suggests *lower tract bleeding* (Table 12.6). The darker urine has had more time to become oxidized in the urinary tract. However, exceptions occur. Rapid upper tract bleeding may be red, and a dissolving clot within the bladder may produce brown urine. Establishing the source of microscopic hematuria can be difficult. *Glomerular bleeding* produces small and dysmorphic RBCs with blebs or burr cells as opposed to the normal-sized RBCs in lower tract bleeding. These changes are best observed with phase-contrast microscopy, which is not readily available in most clinical settings. The presence of significant proteinuria also suggests upper tract (kidney) disease. The presence of even a single RBC or hemoglobin cast indicates a glomerular (or, rarely, tubular) etiology.

Table 12.6 Glomerular and Nonglomerular Hematuria

	GLOMERULAR HEMATURIA	NONGLOMERULAR HEMATURIA
History		
Burning on micturition	No	Urethritis, cystitis
Systemic complaints	Edema, fever, pharyngitis, rash, arthralgia	Fever with urinary tract infections.
Pain	IgA nephropathy—flank pain	Calculi—costovertebral pain, radiating pain to groin
Trauma	No	Bright red urine
Family history	Deafness in Alport syndrome, renal failure	May be positive with calculi
Physical Examination		
Hypertension	Often present	Unlikely
Edema	May be present	No
Abdominal mass	No	Wilms tumor, polycystic kidneys
Rash, arthritis	Lupus erythematosus, Henoch-Schönlein	No
Urinalysis		
Color	Brown, tea, cola	Bright red
Proteinuria	Often present	No
Dysmorphic red blood cells	Yes	No
Red blood cell casts	Yes	No
Crystals	No	May be informative in patients with calculi

IgA, Immunoglobulin A.
Kaplan BS, Pradhan M. Helping the pediatrician to interpret urinalysis. *Pediatr Ann.* 2013;42:45–51.

73. Why does recurrent macroscopic hematuria sometimes “gross” us out?

Gross hematuria is problematic because we may not determine a cause and the uncertainty results in parental anxiety and second/third opinions. The most common diagnoses in children with glomerular gross hematuria are IgA nephropathy and Alport syndrome. No cause will be found in the majority of children with glomerular gross hematuria. The most common diagnoses in patients with nonglomerular gross hematuria are hypercalciuria, urethrorrhagia, and hemorrhagic cystitis. Recurrences of gross hematuria are uncommon. In nearly half of the patients with nonglomerular gross hematuria, no diagnosis can be established, but their long-term prognosis appeared to be good.

Viteri B, Reid-Adam J. Hematuria and proteinuria in children. *Pediatr Rev.* 2018;39(12):573–587.
Youn T, Trachtman H, Gauthier B. Clinical spectrum of gross hematuria in pediatric patients. *Clin Pediatr.* 2006;45:135–141.

74. If a healthy 10-year-old boy has bright red blood at the end of a previously clear urine stream, what is the likely diagnosis?

Urethrorrhagia. In a preadolescent or early adolescent male, terminal hematuria, which may present with bloodstained underpants, often reflects engorged vessels around the entry of the prostatic duct into the urethra at the veru montanum. Although the etiology is unclear, it is a benign condition associated with hormonal changes at adolescence. It resolves spontaneously in weeks to months and does not require cystoscopy or other investigations.

75. A concerned mother of infant twins brings in a diaper from each, with one having pink urine stains and the other blue urine stains. Which is more worrisome?

- *Blue diaper syndrome* is more worrisome because it is a rare, autosomal recessive inborn error of amino acid metabolism caused primarily by defects in tryptophan intestinal absorption. Increased intestinal bacterial degradation of tryptophan results in increased production and absorption of indican (a protein breakdown product). These infants exhibit indicanuria, which on exposure to air oxidizes to an indigo blue color. The condition can be associated with visual problems, hypercalcemia, and nephrocalcinosis.
- *Pink diaper syndrome,* on the other hand, is a benign condition often misinterpreted as hematuria. The red-brown spotting is caused by normal urate crystals, which turn pink on exposure to air and form a powder (unlike blood) that can be scraped from the diaper (unlike blood).

76. What evaluations should be considered during the evaluation of isolated hematuria?

This is a subject of endless debate. There are two main approaches—one is an unfocused approach and the other is a tailored approach. The thoughtful approach considers hematuria as a symptom of a clinical problem. A careful history and examination must be done.

If the urine is coffee or cola colored and proteinuria and RBC casts are present, consider a glomerulonephritis:

- Check BUN, serum creatinine, and electrolytes; serologic studies for evidence of a recent streptococcal infection (unless hematuria is recurrent or present for several months); and serum C3.
- Check ANCA if there is evidence of a vasculitis (fevers, arthralgias, rashes, lung disease).
- Check ANA and DNA-binding activity if there are clinical features of systemic lupus erythematosus (SLE). Isolated hematuria almost never occurs in lupus nephritis.
- Obtain a formal hearing test if there is a family history of Alport disease.

If the urine is bright red and painless:

- Obtain a renal ultrasound to rule out a Wilms tumor or bladder cancer.
- Obtain a renal ultrasound to rule out renal calculi (they are not always painful).
- Obtain a renal ultrasound if there is a history of blunt abdominal trauma to rule out a large renal cyst, dominant polycystic kidney disease, or hydronephrosis.
- Obtain a hemoglobin electrophoresis if sickle cell trait or disease is suspected.

If the urine is bright red with dysuria:

- Obtain a renal ultrasound to rule out renal calculi.
- Obtain a calcium-to-creatinine ratio to rule out hypercalciuria.
- Obtain a urine culture for a bacterial cause if there are symptoms of a UTI.

Brown DD, Reidy KJ. Approach to the child with hematuria. *Pediatr Clin North Am.* 2019;66(1):15–30.

KEY POINTS: MICROSCOPIC HEMATURIA

1. This is a common finding. Asymptomatic microscopic hematuria is detected in 0.5% to 2% of schoolchildren by the dipstick test.
2. Asymptomatic microscopic hematuria is benign in the majority of individuals.
3. Further evaluation is costly and of no value in the absence of proteinuria, RBC casts, or a family history of renal disease or renal calculi.
4. Hypercalciuria ($>$4 mg/kg per day) is the most frequent identifiable cause.
5. Patients with significant proteinuria along with hematuria are much more likely to have underlying pathology.
6. If the dipstick assessment is positive for blood but microscopic urinalysis is negative for RBCs, consider red dyes from beets or candy, hemolysis (hemoglobinuria), or rhabdomyolysis (myoglobinuria).

77. What condition should be suspected in a 9-year-old with a history of hearing loss and visual deficits who presents with hematuria?

Alport syndrome, also known as **hereditary nephritis**, should be considered. The cause is one of several genetic mutations that alter a type IV collagen protein essential for glomerular basement membrane function, for integrity of the inner ear organ of Corti, and for maintaining the shape of the lens. The inheritance pattern is mixed: 80% of cases are X-linked, 15% are autosomal recessive, and 5% are autosomal dominant.

Kashtan C. Alport syndrome: facts and opinions. *F1000Res.* 2017;6:50.

HYPERTENSION

78. How is HTN defined in children?

The diagnosis of HTN is made on the basis of *comparison* with the normal BPs of healthy normal-weight children of a similar age, sex, and height. The American Academy of Pediatrics (AAP) clinical practice guideline, published in 2017, lists normative tables with percentiles and defines BP categories and stages as follows:

For children ages 1 year to < 13 years (in mm Hg):

- Normal BP: <90th percentile
- Elevated BP: ≥90th percentile to 95th percentile or 120/80 to <95th percentile (whichever is lower)
- Stage 1 HTN: ≥95th percentile to 95th percentile + 12 or 130/80 to 139/89 (whichever is lower)
- Stage 2 HTN: ≥95th percentile + 12 or ≥140/90 (whichever is lower)

For children ages ≥ 13 years (in mm Hg):

- Normal BP: <120/<80
- Elevated BP: 120/<80 to 129<80
- Stage 1 HTN: 130/80 to 139/89
- Stage 2 HTN: ≥140/90

Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904.

79. What screening BP values require further evaluation?

See Table 12.7.

Table 12.7 Screening Blood Pressure (BP) Measurements (in mm Hg) That Require Further Evaluation

AGE (YEARS)	SYSTOLIC BP	DIASTOLIC BP
	Boys/Girls	**Boys/Girls**
1	98/98	52/54
2	100/101	55/58
3	101/102	58/60
4	102/103	60/62
5	103/104	63/64
6	105/105	66/67
7	106/106	68/68
8	107/107	69/69
9	107/108	70/71
10	108/109	72/72
11	110/111	74/74
12	113/114	75/75
≥13	120/120	80/80

Adapted from Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904.

Children at or above these numbers should be compared with the full table because a taller child will have higher normal BPs. If elevated, repeat BP measurements are indicated.

KEY POINTS: HYPERTENSION

1. Common causes of artifactual elevation: The BP cuff is too small, the arm is below the level of the heart, the child is talking and feet are off the ground, or the child is given no time to relax.
2. Common causes of artifactual decrease: The arm is above the level of the heart.
3. Essential (no detectable cause): There is often a strong family history of HTN.
4. Secondary (detectable lesion) HTN: The higher the BP and younger the child, the more likely there is a secondary cause for the HTN.
5. Most cases of secondary HTN in children are caused by renal, renal parenchymal, or renovascular disease.

80. Why are repeat visits necessary to diagnose HTN?

Children and adolescents have very **labile BP** with prompt response to internal and external stimuli and will have substantial reductions in BP between the first and third visits to a new doctor, in part because of decreased anxiety. Among patients diagnosed as being hypertensive on a first visit to a new physician, there is a mean 15/7 mm Hg fall in the BP by the third visit, with some patients not reaching a stable value until the sixth visit. This does not apply to children or adolescents with repeat BP measurements that at a *single* visit indicate the presence of stage 2 hypertension (see question 78). These children need immediate evaluation.

81. How do you determine the optimum cuff size for obtaining a BP?

The length of the inflatable bladder inside the cuff (easily palpated) should encircle least 80% of the arm and will overestimate the BP if it is too short. Additionally, the height of the cuff should be the largest size that comfortably fits from the axilla to the elbow. A cuff that is too small will produce falsely elevated BP readings.

82. Who was Korotkoff?

Nikolai Korotkoff was an early twentieth-century Russian vascular surgeon who invented a noninvasive auscultatory method for BP analysis in 1905. He died in 1920 at the age of 46 from pulmonary tuberculosis.

Segall HN. How Korotkoff, the surgeon, discovered the auscultatory method of measuring arterial pressure. *Ann Intern Med.* 1975;83(4):561–562.

83. Which Korotkoff sound best represents diastolic BP?

The *Korotkoff sounds* are produced by the flow of blood as the constricting BP cuff is gradually released. There are *five phases* of Korotkoff sounds. The first appearance of a clear, tapping sound is called *phase I* and represents the systolic pressure. As the cuff continues to be released, soft murmurs can be auscultated; this is *phase II*. These are followed by louder murmurs during *phase III,* as the volume of turbulent blood passing through the partially constricted brachial artery increases. The sounds become abruptly muffled in *phase IV* and disappear in *phase V* (usually within 10 mm Hg of phase IV). In studies that compare intravascular BP determinations with auscultatory readings, true diastolic pressure is most closely related to **phase V** (the disappearance of sound). In some young children, muffled sounds can be heard to "zero" and do not clearly correlate with diastolic pressure. In these instances, it is best to record both the phase IV (the point at which sounds become muffled) and the phase V readings (e.g., 80/45/0).

84. What is ambulatory blood pressure monitoring (ABPM)?

ABPM is a noninvasive technique for measuring multiple BP readings over a 24-hour period during regular activities and during sleep. It has emerged as an increasingly important tool in the diagnosis and management of children with HTN. ABPM is performed using an approved ABPM monitor. An appropriately sized BP cuff is placed on the nondominant arm and attached to a small monitor. For 24 hours, BP recordings are taken every 20 minutes while the patient is awake and every 30 minutes while asleep. ABPM is considered satisfactory if there is a minimum of 40 readings during the 24 hours with at least 6 "sleep" readings.

85. What are the advantages and limitations of ABPM?

- *Advantages:* ABPM measurements are made outside of the health care environment, and multiple parameters of BP can be assessed (mean 24-hour, daytime and nighttime readings, nocturnal dipping, and BP variability). In the general adult population, nocturnal nondipping, nocturnal HTN, and increased BP variability are predictive of cardiovascular morbidity and mortality. ABPM also permits diagnosis of masked HTN (normal office BP but ambulatory BP >95th percentile for sex and height).
- *Limitations:* There is uncertainty about normative BP measures, difficulty in defining ambulatory HTN, technical limitations and costs.

Flynn JT, Daniels SR, Hayman LL, et al. Update: ambulatory blood pressure monitoring in children and adolescents. A scientific statement from the American Heart Association. *Hypertension.* 2014;63(5):1116–1135.

86. In what settings is ABPM particularly useful?

- **White-coat hypertension (WCH):** WCH is defined as BP levels that are $\geq$95th percentile when measured in the office but are completely normal (average BP $<$90th percentile) outside of the clinical setting. Office measurements often fail to account for this transient, stress-induced elevation of BP. WCH is common in children. Children and adolescents with WCH have increased body mass index (BMI) and a tendency toward an elevated left ventricular mass index, thereby strengthening the suggestion for clinical follow-up using ABPM.
- **Masked HTN:** This is the opposite. Patients are truly hypertensive, but the diagnosis is missed in office measurements. The incidence of this phenomenon is usually seen in children with CKD and after solid organ transplantation.

Hanevold CD. White coat hypertension in children and adolescents. *Hypertension.* 2019;73(1):24–30.
Chaudhuri A. Pediatric ambulatory blood pressure monitoring: diagnosis of hypertension. *Pediatr Nephrol.* 2013;28(7):995–999.

KEY POINTS: WAYS TO AVOID MISDIAGNOSING HYPERTENSION

1. Properly sized cuff (age-dependent) with arm supported and kept at heart level
2. Quiet room, quiet patient, seated, feet on the floor or on a stool
3. Repeated measurements over time and the use of averaged values
4. Get rid of the white coat (establish a nonthreatening environment)
5. Sit at the child's level when taking the measurement

87. When should HTN be treated in the neonate?

As a general rule, HTN is defined as a BP $>$90/60 mm Hg in term neonates and $>$80/45 mm Hg in preterm infants, but strict definitions are unavailable given limited data. A sustained systolic BP of $>$100 mm Hg in the neonate should be investigated and treated. The most common cause is renovascular disease.

Batisky DL. Neonatal hypertension. *Clin Perinatol.* 2014;41(3):529–542.

88. What are the indications for the pharmacologic treatment of HTN in children and in adolescents?

- Symptomatic HTN (e.g., headaches, visual disturbances, seizures)
- Stage 2 HTN
- Stage 1 HTN (without target-organ damage) not responding to 4 to 6 months of nonpharmacologic therapy (e.g., weight reduction, exercise, decreased salt intake)
- Secondary HTN
- Hypertensive target-organ damage (left ventricular hypertrophy on echocardiogram)
- Diabetes (types 1 and 2) with BP $\geq$90th percentile

Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904.

89. During the evaluation of a child with elevated BP, what risk factors should be considered for identification and/or reduction?

Important risk factors for HTN in children:

- Family history (If one parent has HTN, the risk is about 25%; if both parents have HTN, the risk is 45%.)
- Genetic factors, including ethnicity (Blacks have twice the incidence of HTN compared with whites, beginning in adolescence.)
- Obesity
- History of renal disease
- Dietary factors (mainly salt intake)
- Low birth weight
- Because HTN is a critical risk factor for cardiovascular disease, additional important cardiovascular risk factors should be assessed. These include diet, serum lipids, tobacco use, and lack of exercise.

90. What historical information suggests a secondary cause of HTN?

- Known UTI; recurrent abdominal or flank pain with frequency, urgency, dysuria; and secondary enuresis are suggestive of a secondary cause of HTN.
- Joint pains, rash, fever, edema suggest a vasculitis.
- A complicated neonatal course requiring use of an umbilical artery catheter suggests renal artery stenosis.
- Renal trauma suggests renal artery stenosis.

- HTN suggested by drug use (sympathomimetics, anabolic or corticosteroids, NSAIDs, oral contraceptives, illicit drugs) may be responsible for drug-induced HTN.
- Aberrant course or timing of secondary sexual characteristics or virilization suggests an adrenal disorder.
- Nervousness, personality changes, sweating, and flushing suggest a pheochromocytoma or hyperthyroidism.

91. What is the most common cause of renal artery stenosis in children in the United States?

Fibromuscular dysplasia, a nonatherosclerotic, noninflammatory arterial disease of unclear cause, is the most common cause. In Asian children, it may be Takayasu arteritis (a vasculitis). This contrasts with adults, for whom atherosclerosis is the most common cause. Gold standard for diagnosis is catheter angiography, but other, less invasive tests, such as computed tomography angiography (CTA), are useful (Fig. 12.3). The vessel narrowing results in afferent arterioles of the kidney sensing a decreased systemic blood pressure due to reduced blood flow. The renin–angiotensin–aldosterone system is activated, which contributes to HTN.

Louis R, Levy-Erez D, Cahill AM, Meyers KE. Imaging studies in pediatric fibromuscular dysplasia (FMD): a single-center experience. *Pediatr Nephrol.* 2018;33(9):1593–1599.

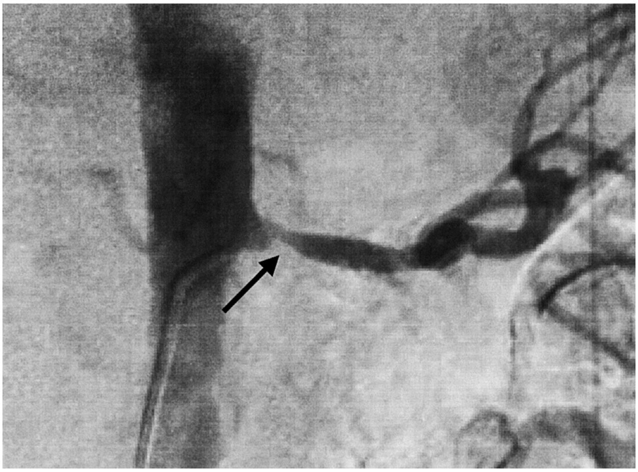

Fig. 12.3 Renal arteriogram showing renal artery stenosis *(arrow)* secondary to fibromuscular dysplasia. (From Kaplan BS, Meyers KEC. *Pediatric Nephrology and Urology: The Requisites in Pediatrics*. Philadelphia, PA: Elsevier Mosby; 2004:119.)

92. List the features on physical examination that suggest a secondary cause of HTN.

See Table 12.8.

Table 12.8 Physical Findings That Suggest a Secondary Cause of Hypertension

PHYSICAL FINDING	POSSIBLE SECONDARY CAUSE
Blood pressure: >140/100 mm Hg at any age	Multiple secondary causes
Leg < arm blood pressure, decreased or delayed leg pulses	Coarctation of the aorta
Adenotonsillar hypertrophy	Obstructive sleep apnea
Muscle weakness	Hyperaldosteronism
Joint swelling	Lupus nephritis, collagen vascular disease
Poor growth	Chronic renal disease
Turner syndrome	Coarctation of the aorta

Continued on following page

Table 12.8 Physical Findings That Suggest a Secondary Cause of Hypertension (*Continued*)

PHYSICAL FINDING	POSSIBLE SECONDARY CAUSE
>5 café au lait spots or neurofibromas	Renal artery stenosis, pheochromocytoma
Bruits over large vessels	Arteritis
Bruits over mid abdomen	Renal artery stenosis
Flank or upper quadrant mass	Renal malformation, renal or adrenal tumor
Excess sweating, increased resting heart rate	Pheochromocytoma, hyperthyroidism
Excessive virilization or secondary sex characteristics inappropriate for age	Adrenal disorder
Edema	Renal disease

93. What categories of antihypertensive medications are used for outpatient management of hypertensive children?

- ACE inhibitors
- ARBs
- Calcium channel blockers (CCBs)
- α-Blockers and β-blockers
- Central α-agonists
- Vasodilators
- Diuretics

Chaturvedi S, Lipszyc DH, Licht C, et al. Pharmacological interventions for hypertension in children. *Cochrane Database Syst Rev.* 2014;2:CD008117.

94. A 12-year-old girl is referred for evaluation of severe HTN. She has hypernatremia, hypokalemia, and metabolic alkalosis, and plasma renin activity (PRA) on an ACE-inhibitor is not detectable. What is the most likely diagnosis?

Low renin monogenic HTN. Arterial HTN in childhood may be due to single-gene mutations inherited in an autosomal dominant or recessive fashion. Consider a genetic cause if there are abnormal potassium levels (low or high) in the presence of suppressed renin secretion and metabolic alkalosis or acidosis.

Simonetti GD, Mohaupt MG, Bianchetti MG. Monogenic forms of hypertension. *Eur J Pediatr.* 2012;171(10):1433–1439.

95. Why should patients with HTN and/or those using diuretics avoid true licorice?

True licorice contains glycyrrhizic acid, which indirectly has mineralocorticoid properties (i.e., fluid and sodium retaining, potassium reducing). However, most American licorice contains only licorice flavoring without any such properties. Some chewing tobacco and chewing gum also contain licorice and have been associated with an excessive mineralocorticoid syndrome. Think of this if you are called to evaluate an edematous Boston Red Sox batboy.

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de Klerk GJ, Nieuwenhuis MC, Beutler JJ. Hypokalaemia and hypertension associated with use of liquorice flavoured chewing gum. *BMJ.* 1997;314(7082):731–732.

PROTEINURIA/NEPHROTIC SYNDROME

96. How does the dipstick test for urine protein compare with the sulfosalicylic method?

- *Dipstick assessment* relies on the reaction of protein (primarily albumin) with tetrabromophenol blue in a citrate buffer impregnated on the dipstick patch. Mild false-positive reactions can occur (1+ to 2+) when the patient's urine is alkaline or when the dipstick is allowed to sit in the urine for too long and the buffer strength is overcome. The results are reported qualitatively as 1+ to 3+, which corresponds to a range of 30 to 500 mg/dL.

- *Sulfosalicylic acid test* precipitates protein in the urine and allows for a comparison with a group of previously prepared aqueous standards; it is reported in the same way as those standards. In contrast with the dipstick assessment, all proteins—not just albumin—are precipitated, as are iodinated contrast material and some antibodies. Finding heavy proteinuria by sulfosalicylic acid testing with minimal proteinuria by dipstick testing suggests the presence of large amounts of nonalbumin protein. This occurs in adults as the result of multiple myeloma and the excretion of Bence Jones proteins and in children in X-linked Dent disease (a renal tubulopathy).

97. What is microalbuminuria (MA)?

MA refers to the presence of small (micro) amounts of albumin in urine. It does not refer to small-sized albumin!

98. In what clinical setting is MA a particularly important finding?

Type 1 diabetes mellitus. Long-term complications include blindness, kidney damage, cardiovascular disease, and neuropathy. Care for persons with diabetes is focused on early detection and prevention of nephropathy, which occurs in 10% to 20% of diabetics. The earliest evidence of nephropathy is MA, defined as the presence of small quantities of albumin in the urine (30 to 300 mg/24 hours). Prompt treatment of MA may delay or prevent complications. A first morning sample is recommended, but a random sample is acceptable. MA may be increased with exercise, illness, HTN, marked hyperglycemia, and diurnal patterns. Therefore it is advisable to obtain three samples over 3 months to avoid false-positive screening results.

Montgomery KA, Ratcliffe SJ, Baluarte HJ, et al. Implementation of a clinical practice guideline for identification of microalbuminuria in the pediatric patient with type 1 diabetes. *Nurs Clin North Am.* 2013;48(2):343–352.

99. What is the best *spot* method for determining the amount of proteinuria?

Urine protein/creatinine excretion ratio (PCR). A 24-hour urine collection for protein is difficult to obtain in children and is imperfect in adults. Although both the dipstick and the sulfosalicylic methods estimate the concentration of protein in urine, small amounts of protein in very concentrated urine will register as more positive than the same amount of protein in dilute urine. The PCR approximates the total 24-hour urinary protein excretion. On a random sample, a PCR of <0.2 to 0.25 reflects normal daily protein excretion, whereas values of >2 suggest the presence of nephrotic-range proteinuria. This test is effective for the diagnosis of the nephrotic syndrome and for follow-up evaluations in children with prolonged and difficult-to-manage proteinuria. However, the test may overestimate protein excretion in individuals with low muscle mass and therefore lower creatinine excretion. Multiplying the ratio by 0.63 gives an approximation for the 24-hour protein excretion in g/m^2 per 24 hours.

100. An asymptomatic 11-year-old boy is found to have 2+ protein on dipstick testing during a routine checkup. How should he be evaluated?

Assuming that he is healthy and without subtle signs of renal disease (e.g., short stature, pallor, HTN), and assuming that this is isolated proteinuria without hematuria, always determine whether the proteinuria is **orthostatic**, **intermittent**, or **persistent**.

- *Intermittent (transient) proteinuria* is entirely benign and does not require any evaluation.
- *Persistent proteinuria* may or may not be benign. The presence of persistent proteinuria can be determined by rechecking the urine at least three times over 2 to 3 weeks. One of these tests should be performed on a first morning urine specimen (ask the child to void before going to bed the night before).
- *Orthostatic proteinuria* is determined in the same way. Orthostatic proteinuria is benign. Causes of transient or orthostatic proteinuria include fever, vigorous exercise, dehydration, stress, cold exposure, and seizures.

101. How is the diagnosis of orthostatic proteinuria established?

By definition, individuals with *orthostatic proteinuria,* who are usually adolescents, have normal rates of protein excretion when recumbent but have increased excretion rates when upright/ambulant. Although all individuals excrete more protein when standing, some have an exaggerated response and may excrete as much as 1 g per day of protein. The adolescent is instructed to empty the bladder before going to bed and collect a first morning urine specimen immediately on arising. Protein excretion is then assessed with a urine dipstick or in the laboratory as the PCR. In a concentrated first morning urine specimen (urine specific gravity ≥ 1.018), a trace or negative value by dipstick assessment or sulfosalicylic acid precipitation rules out proteinuria. At any urine specific gravity, a urine PCR of <0.25 is normal. Remember, even individuals with renal disease may have increased protein excretion when standing and lower protein excretion rates when recumbent. The diagnosis of orthostatic proteinuria requires that protein excretion is truly normal when recumbent, elevated when ambulatory, and the individual is otherwise entirely healthy.

102. What additional evaluation should be done for a patient with persistent proteinuria?

If the proteinuria is persistent and not orthostatic, the **amount of protein excretion** must be determined. A timed 24-hour urine collection may be difficult to obtain in children because variable amounts of urine are often lost. The standard definition of proteinuria is the excretion of >4 mg/m^2 of protein per hour (or 100 mg every 24 hours for a 30-kg child). In practice, however, the urine PCR is used more frequently to assess proteinuria.

The evaluation of a child with persistent proteinuria includes the same tests required to evaluate glomerulonephritis. Staged investigations include:

Stage 1: Assess BUN, serum creatinine, serum electrolytes, serum albumin, C3 and C4 levels.
Stage 2: Assess ANA, anti-DNA antibodies, and ANCA, depending on clinical findings.
Stage 3: Renal imaging studies and renal biopsy may be necessary for diagnosis.

103. What is the natural history of orthostatic proteinuria?

The long-term outcome of children and adolescents is **benign**. Most agree that the prognosis is excellent, although the etiology remains unclear.

104. What level constitutes significant proteinuria?

Protein excretion of **$>$4 mg/m^2 per hour** on a timed urine collection is abnormal. Children with nephrotic syndrome excrete more than 40 mg/m^2 per hour. The upper limit of protein excretion in adults is 150 mg per day, but adolescents may excrete as much as 250 mg per day. A urine protein/creatinine ratio of $>$0.5 in children $<$2 years old and of $>$0.2 in older children is abnormal.

105. In a child with hematuria, can proteinuria be attributed to the protein that is contained in whole blood?

Only in a child with grossly bloody urine. If the urine is normal in color (yellow or clear), any amount of protein above trace is abnormal.

106. Can proteinuria be caused by leukocytes or mucus in the urine?

Probably not, although this untested statement is passed on from one generation of physicians to the next. Regardless of whether mucus or leukocytes can yield a positive dipstick test for albumin, it is important to do a spot protein/creatinine ratio if the test is $>$1+.

107. At what serum albumin concentration does edema develop?

Edema starts to manifest when the serum albumin decreases to **$<$2.5 g/dL**. Edema is almost always present at concentrations of $<$1.8 g/dL unless the child is receiving a diuretic or suffers from the rare condition of congenital analbuminemia (a very rare condition of low levels of albumin due to impaired synthesis but compensated for by increased amounts of other circulating plasma proteins).

108. What is the most common form of nephrotic syndrome in childhood?

Minimal-change nephrotic syndrome (MCNS), previously known as *lipoid nephrosis* and *nil disease,* is the most common form. Most patients with MCNS have favorable therapeutic responses and prognoses. Unfortunately, many have frequent relapses, some are steroid dependent, and a minority are steroid resistant. The etiology of MCNS is unknown, but the pathogenesis is related to abnormal T-lymphocyte function.

109. What is the most important historical factor to consider when assessing a patient for possible MCNS?

The only definitive way to prove MCNS is with a renal biopsy, but this is rarely indicated. **Age at presentation** is the most important characteristic. Between 75% and 80% of children with nephrotic syndrome have MCNS, and about 80% of those present within the first 8 years of life. It is unusual to manifest before a year of age. Early onset in the first 6 months of life suggests a diagnosis of one of the types of congenital nephrotic syndrome or a secondary cause, such as congenital syphilis.

110. What are the typical clinical features and therapeutic responses seen in patients with MCNS?

Edema is generally present, BP is normal to slightly increased, and gross hematuria is absent, but up to one-third may have microscopic hematuria without RBC casts. In the absence of significant intravascular volume depletion, BUN, creatinine, and serum electrolytes are all within normal limits. Serum calcium is low because of hypoalbuminemia. Children who present with these findings should be started on daily prednisone. Up to 90% respond in 1.5 to 4 weeks and have steroid-sensitive nephrotic syndrome (SSNS). A response is indicated by a diuresis and a negative or trace dipstick test for protein. If therapy is prolonged for an additional month, another 4% will respond. About 3% of children with biopsy-proven MCNS will be steroid resistant despite 2 months of therapy.

111. Why is floating in a swimming pool of benefit to older children with nephrotic syndrome?

Weightlessness has been shown to induce a diuresis in children with nephrotic syndrome and was commonly used in the era before diuretics.

112. What are the indications for furosemide and albumin infusions in patients with nephrotic syndrome?

Indications are severe edema with **incapacitating anasarca**, **cellulitis**, **skin breakdown**, or **respiratory embarrassment from pleural effusions**. Albumin alone is helpful for a patient with a rising BUN caused by decreased renal perfusion, which is most often seen after vigorous diuretic therapy. Infusion of a 25% albumin solution at a dose of 0.5 to 1 g/kg of albumin over 1 to 2 hours, followed by furosemide (1 to 2 mg/kg), can be used to induce diuresis in a child with nephrotic syndrome who is unresponsive to furosemide alone. This measure is only temporary because the rise in albumin will lead to increased protein excretion, thereby returning the serum level to the previous steady-state value.

113. Name two important complications of MCNS.

- **Hypercoagulable state**, which may result in sagittal sinus, cavernous sinuses, and renal venous thrombosis
- **Peritonitis** caused by *Streptococcus pneumoniae* or *E. coli*

114. What are key prognostic factors in MCNS?

The most important prognostic feature in MCNS is a **complete response to corticosteroid therapy**. However, even a partial response, with a decrease in protein excretion, appears to improve the prognosis. Persistent proteinuria beyond 4 to 6 weeks is a poor prognostic sign and is an indication for cyclophosphamide or tacrolimus treatment and may be an indication for a kidney biopsy.

115. A 5-year-old child presents with puffy eyes and the laboratory features of nephrotic syndrome, but fails to respond to corticosteroids within 6 weeks. What is the most likely diagnosis?

Focal segmental glomerulosclerosis (FSGS). This important type of nephrotic syndrome (accounting for about 20% of cases in children) can progress to ESRD. FSGS is believed to represent a group of clinical-pathologic syndromes that share a common glomerular lesion, which is identified by renal biopsy (Fig. 12.4). A positive biopsy does not confer a disease diagnosis, but represents the beginning of an exploratory process that may lead to identification of a specific etiology and its appropriate treatment. No causes have been found in many cases, but increasing numbers of genetic causes are being found, most with autosomal recessive (podocin mutations) and others with dominant modes of inheritance (*ACTN4* mutations). These mutations affect podocyte structure, actin cytoskeleton, calcium signaling, and lysosomal and mitochondrial function. HIV nephropathy and morbid obesity are important causes of secondary FSGS. Patients with a genetic cause do not respond to prednisone treatment. Some patients may benefit from ACE inhibitors.

Jefferson JA, Shankland SJ. The pathogenesis of focal segmental glomerulosclerosis. *Adv Chronic Kidney Dis.* 2014;21(5):408–416.

D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med.* 2011;365(25):2398–2411.

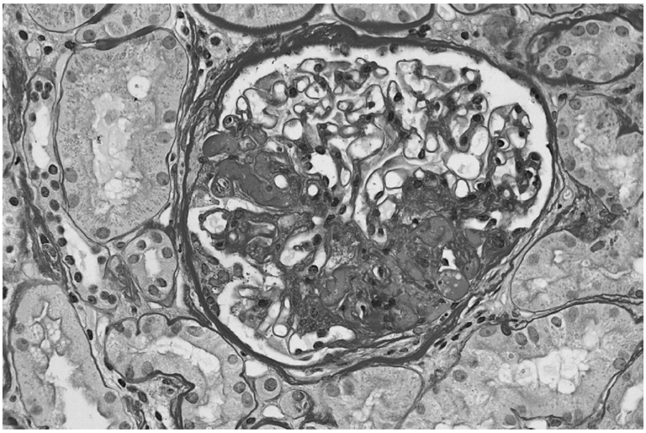

Fig. 12.4 Focal segmental glomerulosclerosis with partial and segmented sclerosis and lesions of increased extracellular matrix and hyalinosis in light microscopic view with periodic acid-Schiff staining. (From Johnson RJ, Fehally J, Floege J, eds. *Comprehensive Clinical Nephrology.* 5th ed. Philadelphia, PA: Saunders;2015:222.)

RENAL FUNCTION ASSESSMENT AND URINALYSIS

116. What is the simplest way to obtain the eGFR in the absence of a timed urine collection?

Devising a simple and reliable eGFR is one of the Holy Grails of nephrology. The previous most-often-used device, the Schwartz formula devised in the mid-1970s, was believed to overestimate GFR. A modified Schwartz formula is now felt to be a more accurate method of estimating GFR. It requires only a serum creatinine concentration and the height of the child in centimeters. No urine collection is necessary. The modified formula is [0.413 × (height in cm/serum creatinine in mg/dL)]. This formula may underestimate eGFR in muscular adolescents and is only validated for CKD stages III through V.

Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20(3):629–637.

117. How can you be confident that a 24-hour urine collection (for any determination) is complete?

Creatinine is produced continuously and is eliminated only through the kidneys. Therefore a given amount, determined largely by muscle mass, will be excreted daily, independent of the level of renal function. Thus the **determination of total urine creatinine** in a timed sample can give a reasonable estimate of whether the collection approximates that of 24 hours. The guidelines for expected creatinine excretion applicable to children and adolescents are as follows: for males, 15 to 25 mg/kg per day; for females, 10 to 20 mg/kg per day.

118. When should routine urinalyses (UA) be performed in the pediatric age group?

There has been some controversy regarding the use of the UA as a routine screening tool. It is a simple, inexpensive, and noninvasive study that is quite sensitive and specific, but the likelihood of this test uncovering significant, previously undiagnosed renal dysfunction is very low. Because of this, the likelihood of false-positive results is high, leading to unnecessary evaluations. In 2007, the AAP made the recommendation to discontinue routine urine dipsticks in healthy children as a screen for CKD.

Sekhar DL, Wang L, Hoffenbeck CS, et al. A cost effectiveness analysis of screening urine dipsticks in well-child care. *Pediatrics.* 2010;125(4):660–663.

American Academy of Pediatrics. Committee on Practice and Ambulatory Medicine: recommendations for preventive pediatric health care. *Pediatrics.* 2007;120(6):1376.

119. What are the maximal and minimal renal dilutional and concentrating capabilities?

Maximally dilute urine has a specific gravity of 1.001 and an osmolality of 50. Maximally concentrated urine has a specific gravity of about 1.032 and an osmolality of about 1200. Urine that is neither concentrated nor dilute (isosthenuric) has a specific gravity of about 1.010 and a corresponding osmolality of 300. Infants born prematurely do not concentrate or dilute urine as effectively as term infants.

120. What is the difference between urine specific gravity and urine osmolality?

Both tests measure the concentration or dilution of the urine, and the relationship between the two is linear and direct, although osmolality is more physiologically correct. *Specific gravity* is determined by the density (and thus the weight and size) of solute in solution. *Osmolality* depends on the number of particles (independent of their size) in solution and their effect on changing its freezing point. Therefore when there are solutes with a relatively large molecular weight (albumin, glucose, contrast material) in the urine, specific gravity will disproportionately increase, and osmolality will be a better indicator of true urine concentration. A urine specific gravity of 1.040 cannot be achieved by the human kidney. Consequently, levels that are high in a child with nephrotic syndrome do not represent supernormal concentrating capacity, but the effect of heavy proteinuria on the specific gravity.

121. Which urinary crystals are always pathologic?

Cystine crystals. These flat, simple, hexagon-shaped crystals are evidence for the amino acid transport disorder cystinuria (Fig. 12.5). In classic cystinuria, the dibasic amino acids (**c**ystine, **o**rnithine, **a**rginine, and **l**ysine: easily remembered as **"coal"**) are affected. The condition would be of little clinical significance except for the fact that cystine is very insoluble and results in nephrolithiasis.

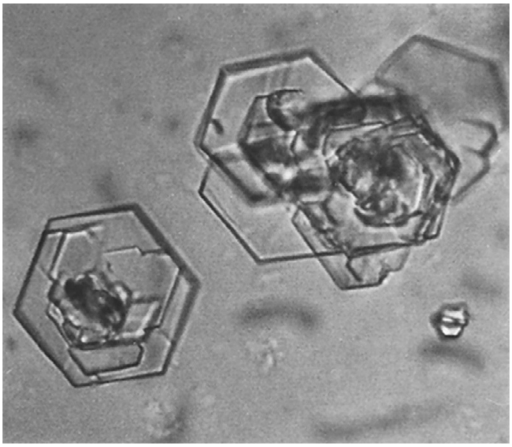

Fig. 12.5 Cystine crystal with hexagonal structure. (From Brown TA, Sonali SJ. *USMLE Step 1 Secrets.* 3rd ed. Philadelphia, PA: Elsevier; 2013:67-96.)

SURGICAL ISSUES

122. What is the most common cause of urinary tract obstruction in the newborn?

Posterior urethral valves are obstructing persistent urogenital membranes, which are often identified prenatally by ultrasound. These occur only in boys. The obstruction is frequently associated with high intravesicular pressures and vesicoureteral reflux (VUR) (Fig. 12.6), which may damage the renal parenchyma, resulting in renal dysplasia if not corrected. Bilateral VUR is a risk factor for poor renal function and ESRD. Thus even with prompt recognition and treatment, renal insufficiency may progress.

Long CJ, Bowen DK. Predicting and modifying risk for development of renal failure in boys with posterior urethral valves. *Curr Urol Rep.* 2018;19(7):55.

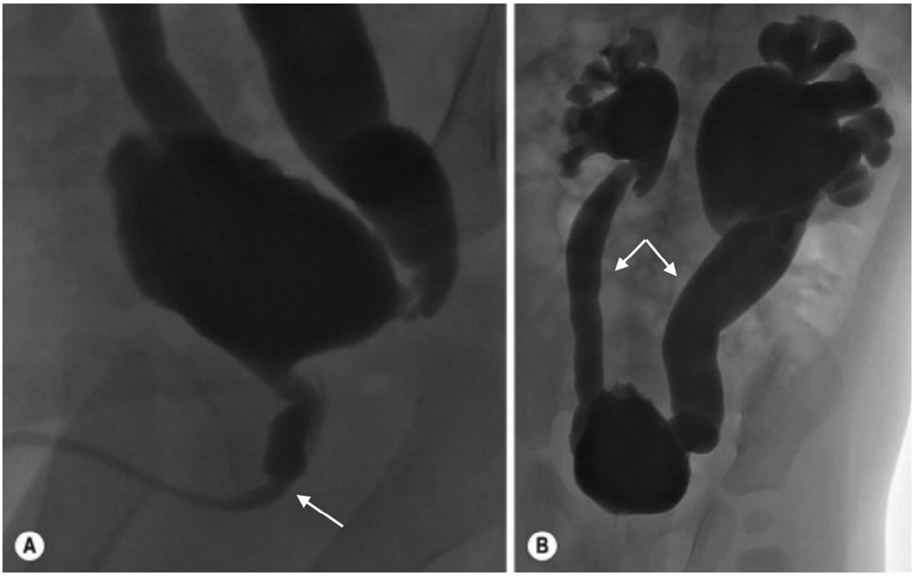

Fig. 12.6 Posterior urethral valves on a voiding cystourethrogram. (A) There is an acute caliber change in the posterior urethra caused by PUV *(arrow)*. (B) Bilateral high-grade ureteral reflux is demonstrated *(arrows)*. (From Adam A, Dixon AK, Gillard JH, Schaefer-Prokop CM, eds. *Grainger & Allison's Diagnostic Radiology.* 6th ed. Philadelphia, PA: Elsevier; 2015:1853.)

123. What is the most common renal abnormality detected on antenatal ultrasound?

Hydronephrosis (also known as **renal pelvic dilatation**), with an incidence between 0.5% and 1% is most common. A renal pelvic diameter $\geq$5 mm is typically viewed as a cutoff point, with grading (0 to IV) of hydronephrosis based on the degree of dilatation, number of calyces observed, and evidence of any parenchymal atrophy. Likelihood of congenital anomalies of the kidney and urinary tract (CAKUT) increases with the severity of hydronephrosis. A repeat ultrasound is advised at 48 to 72 hours and at 4 to 6 weeks after birth. Based on those results, follow-up studies for VUR and urology referral may be required. For patients with isolated antenatal hydronephrosis (without evidence of obstruction), routine prophylactic antibiotics are not indicated. Ninety-eight percent of patients with mild hydronephrosis (renal pelvic diameter $<$12 mm) resolve, stabilize, or improve at follow-up.

Oliveira EA, Oliveira MC, Mak RH. Evaluation and management of hydronephrosis in the neonate. *Curr Opin Pediatr.* 2016;28(2):195–201.

Nguyen HT, Benson CB, Bromley B, et al. Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system). *J Pediatr Urol.* 2014;10(6):982–998.

124. What are the possible pathologic causes of prenatal hydronephrosis?

- Ureteropelvic junction obstruction (most common)
- Posterior urethral valves
- VUR
- Ectopic ureter or ureterocele
- Megaureter (obstructive and nonobstructive)
- Urethral atresia in the prune belly syndrome

125. What is the most common cause of kidney disease of children worldwide?

CAKUT, which includes obstructive uropathies, ureteropelvic junction obstruction, solitary kidney, renal hypoplasia, and VUR, presents as isolated findings or part of genetic syndromes. CAKUT accounts for up to 40% to 50% of cases of ESRD in children and 7% of ESRD in adults. The genetic mutations that cause CAKUT usually are sporadic and have been identified in a variety of signaling pathways regulating nephrogenesis. Currently, <10% of affected patients have identified mutations, and most affected patients may have unique genetic diagnoses. There are presently no benefits of offering genetic testing to patients and their relatives with CAKUT.

Copelovitch L, Furth SL. Genetics and urinary tract malformations. *Am J Kidney Dis.* 2014;63(2):183–185.

126. Is unilateral renal agenesis (URA) a benign condition?

Yes and no. We used to think so, but now we are not so sure. A literature analysis was based on 2684 individuals of whom 63% were males. The incidence of URA was 1 in 2000. Associated CAKUT were identified in 32% of patients, of which VUR was identified in 24% of patients. Extrarenal anomalies were found in 31% of patients. Hypertension was identified in 16% of patients and 21% of patients had microalbuminuria. Ten percent of patients had a lower GFR (<60 mL/min per 1.73 m^2).

Schreuder MF. Life with one kidney. *Pediatr Nephrol.* 2018;33(4):595–604.

Westland R, Schreuder MF, Ket JC, van Wijk JA. Unilateral renal agenesis: a systematic review on associated anomalies and renal injury. *Nephrol Dial Transplant.* 2013;28(7):1844–1855.

127. Should a child with a single kidney be allowed to play football?

This is a frequently asked question. Most pediatric nephrologists prohibit high-contact/collision sports participation by individuals with a single kidney, particularly football. The incidence of catastrophic sports-related kidney injury is 0.4 per 1 million children per year from all sports. Cycling was the most common cause of sports-related kidney injury, causing >3 times the kidney injuries as football. In addition, kidney injury from sports is much less common than catastrophic brain, spinal cord, or cardiac injury. Restricting participation of patients with a single, normal kidney from contact/collision sports is *unwarranted*. Therefore let the family decide. Keep in mind that a large majority of physicians would ban participation, especially in American football.

Grinsell MM, Showalter S, Gordon KA, Norwood VF. Single kidney and sports participation: perception versus reality. *Pediatrics.* 2006;118(3):1019–1027.

TUBULAR DISORDERS

128. In what settings should renal tubular acidosis (RTA) be considered?

Primary RTA is characterized by **chronic hyperchloremic metabolic acidosis** with an inability to acidify the urine and a normal serum anion gap. Primary RTA is separated into three main types. Signs and symptoms that are common with all forms of RTA are growth failure, polyuria, polydipsia, recurrent dehydration, and vomiting. RTA can also occur secondarily to an acquired renal injury.

Santos F, Gil-Peña H, Coto E, et al. Renal tubular acidosis. *Curr Opin Pediatr.* 2017;29(2):206–210.

129. What are defects in each type of primary RTA?

- **Type 1 (distal) RTA:** *Inability of the distal tubule to secrete hydrogen*; in the presence of significant acidosis, urine is not maximally acidified (pH <5.5)
- **Type 2 (proximal) RTA:** *Decreased ability of the proximal tubule to reabsorb filtered* HCO_3 at normal plasma HCO_3 concentrations
- **Type 4 RTA:** Acquired or inherited *tubular insensitivity to aldosterone* or to an *absence of aldosterone*

130. What are the clinical and laboratory features of the primary RTAs?

See Table 12.9.

Table 12.9 Clinical and Laboratory Manifestations of Various Renal Tubular Acidoses

	TYPE 1 (CLASSIC DISTAL)	TYPE 2 (PROXIMAL)	TYPE 4 (ALDOSTERONE DEFICIENCY)
Growth failure	+++	++	+++
Serum potassium	Normal or low	Normal or low	High
Nephrocalcinosis	Frequent	Rare	Rare
Low citrate excretion	+++	±	±
Fractional excretion of filtered HCO_3 at normal serum HCO_3 levels	$<5\%$	5%-10%	$<10\%$
Daily alkali treatment (mEq/kg)	1-3	5-20	1-3
Daily potassium requirement	Decreases with correction	Increases with correction	
Urine pH	>5.5	<5.5	<5.5
Presence of other tubular defects	Rare	Common	Rare

131. How is determining the urine anion gap helpful in the evaluation of MA?

Investigation of any child with a persistent MA must consider some form of RTA in the differential diagnosis. The urinary anion gap is a convenient and accurate screening test for RTA. It is an indirect estimate of *urinary ammonium excretion* (and thus urinary acid excretion) and is calculated by the following formula after determining urinary electrolyte concentrations:

$$\text{Urinary anion gap} = Na^{+} + K^{-} - Cl^{-}$$

If the anion gap is negative, it suggests a large chloride excretion and thus adequate ammonium excretion. The urinary anion gap is negative in hyperchloremic MA as a result of diarrhea, untreated proximal RTA, or prior administration of an acid load. If the anion gap is positive, it suggests an acidification defect, as is seen in patients with distal RTA. Results are not reliable if there are large amounts of unmeasured anions, such as ketoacids, penicillin, or salicylates.

132. How is RTA diagnosed with utilizing a urine anion gap in a patient with a hyperchloremic MA and a normal serum anion gap?

See Fig. 12.7.

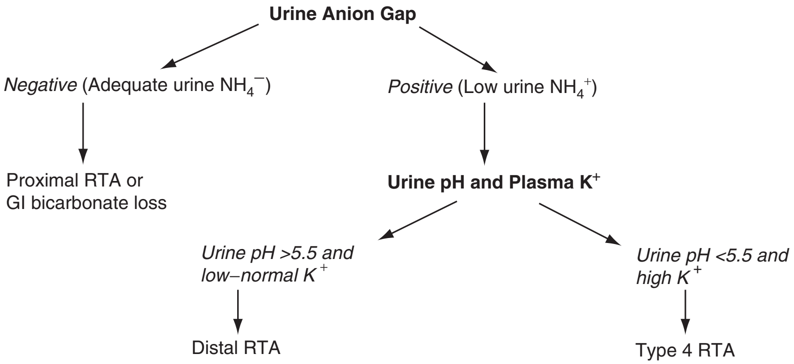

Fig. 12.7 Diagnosis of renal tubular acidosis in patients with hyperchloremic metabolic acidosis and normal serum anion gap. *GI,* Gastrointestinal; *RTA,* renal tubular acidosis. (Adapted from Lash JP, Arruda JA. Laboratory evaluation of renal tubular acidosis. *Clin Lab Med.* 1993;13:117-129.)

133. What is the recommended alkali therapy for the treatment of various forms of RTA?

The goals of RTA therapy are to improve growth, correct MBD, prevent nephrolithiasis and nephrocalcinosis, and control underlying disease processes. *Alkali therapy* (sodium citrate or sodium bicarbonate) is required for all forms of RTA, with the goal of normal plasma HCO_3 level. Patients with distal RTA generally require only 2 to 3 mEq of alkali/kg per day. However, infants may also experience some increased urinary bicarbonate wasting and require up to 10 mEq/kg/day. Patients with proximal RTA require large quantities of alkali (5 to 20 mEq/kg per day). For type 4 RTA, patients usually need low-dose alkali therapy (1 to 3 mEq/kg per day) plus a potassium-restricted diet and mineralocorticoid therapy if there is hypoaldosteronism.

134. What is most common cause of *renal* Fanconi syndrome?

Renal Fanconi syndrome (distinct from *hematologic* Fanconi anemia) is the manifestation of multiple disorders of transport in the proximal tubule. It is characterized by the abnormal excretion of substances normally reabsorbed by the proximal tubule and for which there is no distal mechanism sufficient to recapture the unabsorbed molecules. Thus there is abnormal excretion of glucose, phosphate, potassium, amino acids, and bicarbonate. The phosphaturia and hypophosphatemia result in MBD. Bicarbonate loss causes MA. **Cystinosis**, a lysosomal storage disease with abnormal accumulation of the amino acid cystine, is the most common cause. Consider galactosemia, tyrosinemia, and fructose intolerance in any neonate or infant with severe jaundice, acidosis, and glucosuria, which could be a presentation of renal Fanconi syndrome.

Foreman JW. Fanconi syndrome. *Pediatr Clin North Am.* 2019;66(1):159–167.

135. A 2-year-old girl, generally healthy with height just below the fifth percentile, was noted to have blinking problems and glucose in her urine. Can you connect the two in a single diagnosis?

Patients with **cystinosis** can have photophobia and renal Fanconi syndrome. Cystine-depleting medical therapy and kidney transplantation have transformed this previously fatal disease into a treatable disorder with a life expectancy of $>$50 years. Early diagnosis and appropriate therapy are critically important.

Veys KR, Elmonem MA, Arcolino FO, et al. Nephropathic cystinosis: an update. *Curr Opin Pediatr.* 2017;29(2):168–178.
Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. *Pediatr Nephrol.* 2013;28(1):51–59.

136. Glucosuria is detected on repeated urine dipstick testing in a 5-year-old boy, but the blood glucose is always normal. What is going on here?

In the absence of clinical symptoms, hypokalemia, MA, or an elevated serum creatinine, the diagnosis is **renal glucosuria**. This is a benign condition. Because it is commonly familial, genetic abnormalities in renal glucose reabsorption are the likely culprit. Mild glucosuria is typical; heavy glucosuria is rare.

137. What is the clinical presentation of acute interstitial nephritis (AIN)?

AIN is caused by an immune-mediated inflammatory response that initially involves the renal interstitium and tubules, usually sparing the glomeruli and vasculature. AIN has a wide array of clinical presentations that range from isolated tubular disorders (e.g., Fanconi syndrome) to acute renal failure. Polydipsia with polyuria may be present. Additional findings—fever, rash, and arthralgias—may suggest a hypersensitivity reaction.

138. What medications are causes of AIN?

- Antibiotics, especially penicillin analogs, cephalosporins, sulfonamides, and rifampin
- NSAIDs
- Diuretics, especially thiazides and furosemide
- Proton pump inhibitors

Blank ML, Parkin L, Paul C, Herbison P. A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. *Kidney Int.* 2014;86(4):837–844.

139. What laboratory abnormalities are seen in patients with AIN?

The urine sediment is often bland and may be normal, aside from a low specific gravity.

- Urinary sediment: May contain RBCs, leukocytes (eosinophils), leukocyte casts
- Urinary protein excretion: $<$1 g per day; with NSAID use, may be $>$1 g per day
- Fractional excretion of sodium: Usually $>$1%
- Proximal tubular defects: Glucosuria, bicarbonaturia, phosphaturia, aminoaciduria
- Distal tubular defects: Hyperkalemia, sodium wasting
- Medullary defects: Sodium wasting, urinary-concentrating defects

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Raghavan R, Eknoyan G. Acute interstitial nephritis—a reappraisal and update. *Clin Nephrol.* 2014;82(3):149–162.

URINARY TRACT INFECTIONS

140. What two features on the dipstick test are used to evaluate possible UTIs?

- **Nitrite:** This test examines urine for the possible presence of nitrites, which can be produced by bacteria possessing the enzyme nitrate reductase, which reduces nitrates to nitrites. False negatives can occur. Not all urinary pathogens possess the enzyme (e.g., certain *Serratia* species). The test is more likely to be positive in the setting of a UTI if urine has been present in the bladder for several hours. The test is less effective in infants because of their increased micturition frequency.
- **Leukocyte esterase:** This enzyme, present in white blood cells (WBCs), is typically present when urine is infected. However, because pyuria can be due to other nonbacterial causes and even NSAIDs, the test is less specific.

141. How helpful are dipstick testing and microscopic analysis of urine as screening tests for UTIs?

Sensitivity is the probability that test results will be positive among patients who have UTIs, and specificity is the probability that test results will be negative among patients who do not have UTIs. The sensitivity and specificity of the components of the urinalysis individually and in combination as screening tools for the diagnosis of a UTI are summarized in Table 12.10. Dipstick testing, in particular, is much more effective as a diagnostic tool for UTIs in children >2 years than in younger children.

Mori R, Yonemoto N, Fitzgerald A. Diagnostic performance of urine dipstick testing in children with suspected UTI: a systematic review of relationship with age and comparison with microscopy. *Acta Paediatr.* 2010;99(4):581–584.

Table 12.10 Rapid Screening Tests for Urinary Tract Infection in Children: Sensitivity and Specificity

MICROSCOPY	SENSITIVITY (%) (RANGE)	SPECIFICITY (%) (RANGE)
≥5 WBC/HPF	67 (55, 88)	79 (77, 84)
Any bacteria/HPF	81 (16, 99)	83 (11, 100)
≥5 WBC or bacteria/HPF	99 (97, 100)	65 (67, 74)
DIPSTICK		
Any LE	83 (64, 89)	84 (71, 95)
Any nitrite only	50 (16, 72)	98 (95, 100)
Any nitrite or LE	88 (71, 100)	93 (76, 98)

HPF, High-power field; *LE,* leukocyte esterase; *WBC,* white blood cell.
Data from Christensen AM, Shaw K. Urinary tract infection in childhood. In Kaplan BS, Meyers KEC, eds. *Pediatric Nephrology and Urology: The Requisites in Pediatrics.* Philadelphia, PA: Elsevier/Mosby; 2004:320.

142. Can the diagnosis of UTI be made on the basis of urinalysis alone?

No. A urine culture is the only accurate means of diagnosing a UTI. Urinalysis is valuable for selecting individuals for the prompt initiation of treatment while awaiting results of the urine culture. In older children (in whom UTI symptoms are more reliable indicators of infection), a negative nitrite test, a negative leukocyte esterase test, and the absence of UTI symptoms are highly correlated with the absence of infection. However, babies require a culture to exclude UTI.

KEY POINTS: URINARY TRACT INFECTION

1. *E. coli* bacteria cause 90% of cases.
2. Antibiotic sensitivity testing is important because of the increasing incidence of ampicillin-resistant *E. coli.*
3. Infections may be caused by bacteria ascending from the urethral area.
4. Clean bagged specimens are unreliable for diagnosis because of their high contamination rate.
5. Uncircumcised male infants have a 10-fold greater risk for infection than circumcised male infants.

143. What bacterial counts constitute a positive urine culture?

- **Suprapubic aspiration**: ≥100 colony-forming units (CFU)/mL
- **Catheterization**: ≥10,000 CFU/mL

- **Midstream clean catch**: $\geq$100,000 CFU/mL of a single organism; 10,000 to 100,000 CFU/mL is suspicious for a UTI and requires reculturing; $<$10,000 CFU/mL usually indicates contamination
- **Urine bag**: May be helpful if negative, but even when counts are $\geq$100,000 CFU/mL, there is a 40% to 85% false-positive result

144. A child has painful, frequent urination, and a culture revealed a UTI, but the original UA had a negative nitrite study. What is the most likely reason?

Members of the gram-negative, rod-shaped *Enterobacteriaceae* family can reduce dietary nitrate to nitrite. However, the bacteria need hours for this conversion to occur. A first morning void is more likely to be positive compared with the UA of a child who has been urinating frequently with insufficient time spent in the bladder. A false-negative result is common with the nitrite test.

Patel HP. The abnormal urinalysis. *Pediatr Clin North Am.* 2006;53(3):325–337.

145. What factors can cause a low colony count despite a definite urinary infection?

- High urine volume
- Recent antimicrobial therapy
- Fastidious and slow-growing organisms (enterococci, *Staphylococcus saprophyticus*)
- Low urine pH ($<$5.0) and specific gravity ($<$1.003)
- Bacteriostatic agents in the urine
- Complete obstruction of a ureter
- Chronic or indolent infection
- Use of inappropriate culture techniques

Bock GH. Urinary tract infections. In Hoekelman RA, Adam HM, Nelson HM, et al, eds. *Primary Pediatric Care.* 4th ed. St. Louis, MO: Mosby; 2001:1896.

146. Why should urine specimens be refrigerated if they cannot be immediately processed?

Storage of urine specimens at room temperature is one of the most common causes of false-positive results. At room temperature, enteric organisms in specimens have a growth-doubling time of 12.5 minutes, and thus colony counts become an unreliable guide. If a urine specimen cannot be processed within 15 minutes, it should be refrigerated at $<$39.2°F (4°C) to stop *in vitro* bacterial replication.

147. What are the common presenting signs and symptoms of a UTI in an infant?

The presenting findings are nonspecific and include fever, vomiting, diarrhea, irritability, hyperbilirubinemia (direct or indirect), and poor feeding. These same findings are often seen in infants without UTIs, underscoring the importance of urine cultures in febrile infants.

148. How common are UTIs in young febrile infants?

In infants and toddlers between 2 and 24 months with unexplained fever ($>$100.9°F [38.3°C]), the prevalence is about 7%, but it ranges between 2% and 9%, depending on age and sex. The younger the child, the more likely the presence of a UTI. Girls have twice as many infections (or more) as circumcised boys. White female infants are twice as likely to have a UTI as black infants. In the first 3 months of life, uncircumcised males with fever have a 10-fold increased risk compared with circumcised boys. In infants younger than 2 months, 7.5% are likely to have UTIs, with boys having more infections than girls. Needless to say, the possibility of a UTI should always be considered in younger infants, particularly those without an identifiable source of infection, because UTIs constitute the most likely source of an occult bacterial infection by a wide margin.

Greenhow TL, Hung YY, Herz AM, et al. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J.* 2014;33(6):595–599.

Shaikh N, Morone ME, Bost JE, et al. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J.* 2008; 27(4):302–308.

149. What pathogens are associated with UTIs in children?

Between 80% and 90% of initial UTIs are caused by *E. coli*. Other organisms include *Proteus mirabilis, Klebsiella pneumoniae, Pseudomonas, Enterobacter,* and some *Staphylococcus* species.

150. How is cystitis distinguished clinically from pyelonephritis?

This can be difficult. *Pyelonephritis* tends to have more constitutional symptoms, such as fever, rigors, flank pain, and back pain, whereas *cystitis* has more bladder symptoms, such as enuresis, dysuria, frequency, and urgency. The presence of WBC casts or impaired urinary-concentrating ability is more indicative of pyelonephritis. Patients with pyelonephritis tend to have higher sedimentation rates, C-reactive protein levels, and serum procalcitonin levels, but these results can also be seen in some patients with cystitis. Renal dimercaptosuccinic acid (DMSA) scintigraphy may be useful for identifying acute pyelonephritis. However, for most children, the treatments for cystitis and for pyelonephritis are the same.

151. What is the diagnostic approach for a possible UTI for a female infant 3 to 24 months of age with no known urinary tract abnormalities?

One algorithmic approach uses risk factors and likelihood ratios (a number <1 is less likely, >1 more likely) and UA results to categorize the probability of UTI (Fig. 12.8). Additional diagnostic algorithms are also available at the *JAMA* reference for febrile males ages 3 to 24 months and for verbal children >24 months with urinary or abdominal symptoms.

Schmidt B, Copp HL. Work-up of pediatric urinary tract infection. *Urol Clin North Am.* 2015;42(4):519–526.

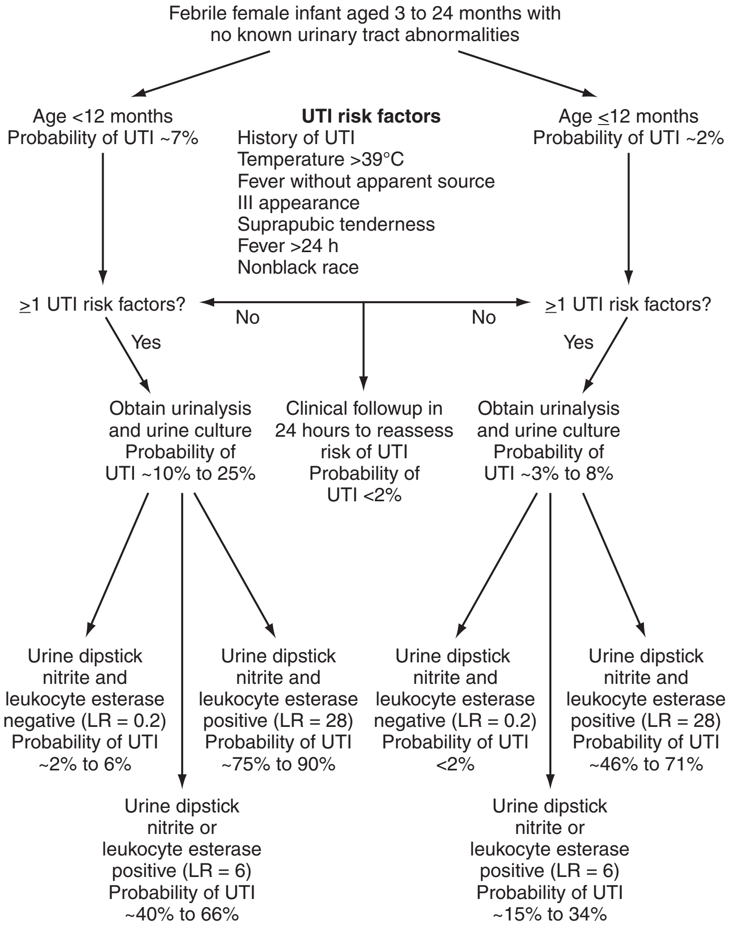
Febrile female infant aged 3 to 24 months with no known urinary tract abnormalities
Age <12 months Probability of UTI ~7%
UTI risk factors
History of UTI
Temperature >39°C
Fever without apparent source
Ill appearance
Suprapubic tenderness
Fever >24 h
Nonblack race
Age ≤12 months Probability of UTI ~2%
≥1 UTI risk factors?
No
No
≥1 UTI risk factors?
Yes
Yes
Obtain urinalysis and urine culture Probability of UTI ~10% to 25%
Clinical followup in 24 hours to reassess risk of UTI Probability of UTI <2%
Obtain urinalysis and urine culture Probability of UTI ~3% to 8%
Urine dipstick nitrite and leukocyte esterase negative (LR = 0.2) Probability of UTI ~2% to 6%
Urine dipstick nitrite and leukocyte esterase positive (LR = 28) Probability of UTI ~75% to 90%
Urine dipstick nitrite and leukocyte esterase negative (LR = 0.2) Probability of UTI <2%
Urine dipstick nitrite and leukocyte esterase positive (LR = 28) Probability of UTI ~46% to 71%
Urine dipstick nitrite or leukocyte esterase positive (LR = 6) Probability of UTI ~40% to 66%
Urine dipstick nitrite or leukocyte esterase positive (LR = 6) Probability of UTI ~15% to 34%

Fig. 12.8 Diagnostic algorithm for febrile female infants 3 to 24 months of age suspected of having a urinary tract infection. *LR,* Likelihood ratio; *UTI,* urinary tract infection. (From Shaikh N, Morone NE, Lopez J. Does this child have a urinary tract infection? *JAMA.* 2007;298:2902.)

152. Which patients with UTIs require hospitalization and parenteral antibiotics?

- Any patient who is toxic, dehydrated, or unable to tolerate oral antibiotics
- A patient with an underlying urinary tract abnormality in which pyelonephritis is suspected
- A patient who is immunocompromised or immunosuppressed

- Many centers will hospitalize any infant <2 months because of a concern of an increased risk for urosepsis or other serious concomitant infections. However, studies indicate that low-risk infants (i.e., not clinically ill, no significant past medical history, normal WBC indices) may be at very low risk for bacteremia or clinical decompensation and might be managed with brief hospitalization or as outpatients. That debate is ongoing.

Chaudhari PP, Monuteaux MC, Bachur RG. Management of urinary tract infections in young children: balancing admission with the risk of emergency department revisits. *Acad Pediatr.* 2019;19(2):203–208.
Schnadower D, Kuppermann N, Macias CG, et al. Outpatient management of young febrile infants with urinary tract infections. *Pediatr Emerg Care.* 2014;30(9):591–597.
Schnadower D, Kuppermann N, Macias CG, et al. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics.* 2010;126(6):1074–1083.

153. Should all pediatric patients with clinical pyelonephritis be hospitalized?

The short- and long-term outcomes of patients (even as young as 2 months old) with uncomplicated pyelonephritis are the same whether they are treated initially with IV antibiotics or with oral, third-generation cephalosporins. A decision about outpatient therapy mandates the ability to tolerate oral antibiotics with no concerns regarding compliance and careful and reliable follow-up.

Morello W, La Scola C, Alberici I, Montini G. Acute pyelonephritis in children. *Pediatr Nephrol.* 2016;31(8):1253–1265.
Strohmeier Y, Hodson EM, Willis NS, et al. Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev.* 2014;7:CD003772.

154. What is the expected resolution of fever after a child is started on an antibiotic for a UTI?

In one study of 128 infants younger than 60 days with UTI treated with parenteral antibiotics, 85% became afebrile within 24 hours. Only 4% were febrile after 48 hours. In another study of 364 patients 1 week to 18 years of age, 32% had fever beyond 48 hours. Older age is a risk factor for protracted fever.

Dayan PS, Hanson E, Bennett JE, et al. Clinical course of urinary tract infections in infants younger than 60 days of age. *Pediatr Emerg Care.* 2004;20(2):85–88.
Currie ML, Mitz L, Raasch CS, et al. Follow-up urine cultures and fever in children with urinary tract infection. *Arch Pediatr Adolesc Med.* 2003;157(12):1237–1240.

155. What is the duration of antibiotic therapy for a UTI?

Data to support a precise duration are insufficient. Standard duration of therapy for cystitis/lower UTIs varies from 7 to 14 days (oral or combined oral plus parenteral). Some experts lean toward 14 days of treatment for pyelonephritis. When IV antibiotics are given, a short IV course (2 to 4 days) followed by oral antibiotics is as effective as a longer course (7 to 10 days) of IV therapy. If the patient has not clinically improved within 2 to 3 days of starting therapy, the urine culture should be repeated and antibiotics adjusted, if indicated. Short-course (2- to 4-day) therapy compared with standard-duration (7- to 14-day) therapy for lower UTIs has shown clinical equivalency in some studies. Single-day or single-dose therapy is less effective and is not recommended.

Strohmeier Y, Hodson EM, Willis NS, et al. Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev.* 2014;7:CD003772.
Fitzgerald A, Mori R, Lakhanpaul M, et al. Antibiotics for treating lower urinary tract infection in children. *Cochrane Database Syst Rev.* 2012;8:CD006857.

156. Are repeat cultures required at the end of therapy for a patient without symptoms?

Although done commonly in the past as a “test of cure,” follow-up urine cultures for a clinically improving patient >2 months of age are **not indicated** because the yield is extremely low (<0.5%).

Oreskovic NM, Sembrano EU. Repeat urine cultures in children who are admitted with urinary tract infections. *Pediatrics.* 2007;119(2):e325–e329.

157. In what patients are prophylactic antibiotics indicated for UTIs?

This is controversial. Prophylaxis for recurrent UTI may reduce the risk for repeat symptomatic UTI, but the benefit is small. Risk for microbial resistance is increased. Recommendations are watchful waiting and rapid assessment when clinical concerns arise. It is also unclear whether preventing recurrent UTIs will prevent renal scarring. Consequently, prophylaxis for recurrent UTI in children *with normal urinary tract anatomy* is debatable, particularly for younger infants.

Prophylaxis is generally indicated:

- In infants or children with their first UTI who have finished their first course of antibiotic therapy and are awaiting the completion of studies (e.g., renal ultrasound).

- In patients with known urologic abnormalities that place them at high risk for recurrent UTIs (e.g., severe voiding disorders, high-grade vesicourethral reflux); however, the value of antibiotics in these situations is also questioned.

Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. *Cochrane Database Syst Rev.* 2019;4:CD001534.

Selekman RE, Shapiro DJ, Boscardin J, et al. Uropathogen resistance and antibiotic prophylaxis: a meta-analysis. *Pediatrics.* 2018;142(1):e20180119.

158. Is cranberry juice helpful in the management of recurrent UTIs in children?

The use of cranberry juice as a urine-acidifying agent and treatment for UTI has been popular for adults since the 1920s and was used in the 1800s for disorders of the bladder. Studies of adults have shown it to be helpful for diminishing the frequency of bacteriuria, possibly because of its antiadhesive properties against *E. coli.* Results in pediatric studies are mixed, but more highly concentrated juice may have some limited value in recurrent UTI in children with no urologic abnormalities.

Durham SH, Stamm PL, Eiland LS. Cranberry products for the prophylaxis of urinary tract infections in pediatric patients. *Ann Pharmacother.* 2015;49(12):1349–1356.

Afshar K, Stothers L, Scott H, MacNeily AE. Cranberry juice for the prevention of pediatric urinary tract infection: a randomized controlled trial. *J Urol.* 2012;188(4 Suppl):1584–1587.

159. Do patients with an initial UTI require imaging studies?

Approaches are controversial because of uncertainties regarding any causal relationship between UTIs, VUR, and renal scarring. In 1999, AAP guidelines recommended renal ultrasonography and voiding cystourethrogram (VCUG) in children <2 years with a UTI to search for anomalies or the presence of VUR. In 2011, these AAP guidelines were revised to recommend a follow-up ultrasound in all cases, but no VCUG routinely after the first UTI. A VCUG was recommended only if ultrasonography revealed hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy. VCUG was also recommended in atypical or complex circumstances and for recurrent UTIs. The value of these studies, particularly their role in preventing long-term renal sequelae, continues under reexamination. Since the revised guidelines, clinical trends do indicate a more limited use of imaging studies with emphasis on higher-risk patients and a reduction in the use of the VCUG. Guidelines in the United Kingdom rely on ultrasound and radionuclide studies rather than the VCUG.

Okarska-Napierala M, Wasilewska A, Kuchar E. Urinary tract infection in children: Diagnosis, treatment, imaging—comparison of current guidelines. *J Pediatr Urol.* 2017;13(6):567–573.

Roberts KB, Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics.* 2011;128(3):595–610.

160. What imaging studies can be used for patients with UTIs who warrant evaluation?

- **Renal ultrasound**, to screen for urinary tract obstruction or other structural genitourinary abnormalities
- **VCUG or radionuclide cystogram**, to evaluate for VUR (the most common abnormality found in children with UTIs)
- **Renal cortical DMSA or MAG-3 (^{99m}Tc-mercaptoacetyltriglycine) scanning**, recommended by some authorities to determine whether there is evidence of acute pyelonephritis or permanent renal scarring (Fig.12.9)

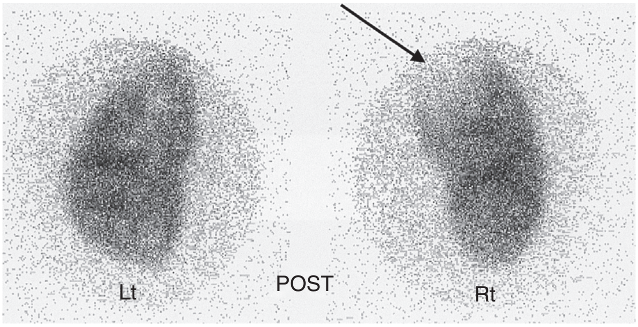

Fig. 12.9 DMSA renal scan showing renal scarring *(arrow)* from pyelonephritis. *Lt,* left; *Rt,* right. (From Kaplan BS, Meyers KEC. *Pediatric Nephrology and Urology: The Requisites in Pediatrics.* Philadelphia, PA: Elsevier Mosby; 2004:119.)

UROGENITAL ISSUES

161. What risks are associated with circumcision?

Rare complications are bleeding and infection. With poor technique, injury or amputation of the glans can occur. Meatal stenosis as a consequence of meatal ulceration is another potential complication.

162. Is circumcision now medically indicated?

We have watched the AAP's position statements on circumcision transform over the past 40 years. In the 1970s, circumcision was viewed as more of a negative. In 1999, the stance was modified to one of neutrality. In a 2012 policy statement, the positive benefits of circumcision were emphasized. Benefits have been found to exceed risks by up to 200 to 1 and over the course of a lifetime, half of uncircumcised males will require treatment for a medical condition associated with retention of the foreskin. These benefits included protection against UTIs, sexually transmitted infections (particularly HIV infections), balanitis, and phimosis and a lower incidence of penile cancer. No study has identified any adverse effect on sexual function or pleasure.

Although medical benefits can be emphasized, the decision at present still rests primarily on nonmedical family and cultural considerations. Data from 2013 from the indicated that the circumcision rate in the United States was about 80%. Clear racial differences were documented, with rates of 91% among whites, 76% among blacks, and 44% among Hispanics.

Morris BJ, Kennedy SE, Wodak AD, et al. Early infant male circumcision: systematic review, risk-benefit analysis, and progress in policy. *World J Clin Pediatr.* 2017;6(1):89–102.
Friedman B, Khoury J, Petersiel N, et al. Pros and cons of circumcision: an evidence-based review. *Clin Microbiol Infect.* 2016;22(9):768–774.
American Academy of Pediatrics Task Force on Circumcision. Circumcision policy statement. *Pediatrics.* 2012;130(3):e756–e785.

163. What distinguishes phimosis and paraphimosis?

- *Phimosis* is a narrowing of the distal foreskin, which prevents its retraction over the glans of the penis. In newborns, retraction is difficult because of normal adhesions that gradually self-resolve. Chronic inflammation or scarring can cause true phimosis with persistent narrowing and may require circumcision.
- *Paraphimosis* is incarceration of a retracted foreskin behind the glans. It occurs when the retracted foreskin is not repositioned. Progressive edema results, which, if uncorrected, can lead to ischemic breakdown. Local anesthesia, ice, and manual reduction usually correct the problem, but if these are unsuccessful, surgical reduction is necessary.

Huang CJ. Problems of the foreskin and glans penis. *Clin Pediatr Emerg Med.* 2009;10:56–59.

164. What is hypospadias?

Hypospadias is a congenital defect in which the urethral opening is displaced to the underside of the penis. It results from the failure or delay of the midline fusion of the urethral folds. It is often associated with a ventral band of fibrous tissue (chordee) that causes ventral curvature of the penis, especially with an erection. Incidence is 1 to 2 per 1000 live births. When assessing hypospadias, it is useful to describe where the urethral meatus appears (i.e., glandular, distal shaft, proximal shaft, or perineal) and also the degree and location of chordee. The treatment of hypospadias is surgical repair, usually as a one-step procedure. With the advent of microsurgical techniques, the optimal time for repair appears to be 6 to 12 months of age.

165. How common are undescended testicles at birth?

The answer is very much dependent on gestational age. About 3% of term male infants are affected, but that increases to up to one-third of premature infants. The more premature the infant, the higher the likelihood of an undescended testicle.

166. When should undescended testicles be repaired?

The optimal time for surgery on an undescended testicle is **≤12 months of age but not <6 months**. Traditional teaching is that the majority of newborn cryptorchidism resolves without intervention, with 75% of full-term infants and 90% of preterm cryptorchid newborns having full testicular descent by the age of 9 months. Some newer studies suggest the rate of spontaneous descent may be lower. Spontaneous descent after 9 months is unlikely. The AAP recommends surgery around 1 year of age to prevent testicular degeneration, to optimize fertility potential, and to decrease the risk for testicular cancer. During the second year of life, ultrastructural changes in the seminiferous tubules of the undescended testes begin to appear, but these may be halted by orchiopexy.

Holland AJ, Nassar N, Schneuer FJ. Undescended testes: an update. *Curr Opin Pediatr.* 2016;28(3):388–394.
Chan E, Wayne C, Nasr A. Ideal timing of orchiopexy: a systematic review. *Pediatr Surg Int.* 2014;30(1):87–97.
Wenzler DL, Bloom DA, Park JM. What is the rate of spontaneous testicular descent infants with cryptorchidism? *J Urol.* 2004;171:849–851.

167. How do you treat labial adhesions?

Labial adhesions are a relatively common gynecologic finding in girls between 4 months and 6 years of age. They may be complete or partial and are thought to result from local inflammation in a low-estrogen setting with resulting skin agglutination. Treatment consists of eliminating the underlying inflammation (if caused by an infection), sitz baths twice daily, maintenance of good perineal hygiene, and topical application of a 1% conjugated estrogen cream over the entire adhesion at bedtime for 3 weeks. The use of estrogen has an 80% to 90% cure rate and may be followed by the application of a petroleum jelly for 1 to 2 months nightly. It should be noted that the natural history of untreated asymptomatic labial adhesions is self-resolution: 50% resolve within 6 months, and nearly 100% resolve by 18 months. Surgical correction is almost never required.

Bacon JL, Romano ME, Quint EH. Clinical recommendation: labial adhesions. *J Pediatr Adolesc Gynecol.* 2015;28(5):405–409.

UROLITHIASIS

168. Why are kidney stones increasing in frequency in children in the United States?

There has been a five fold increase over the past two decades. A leading theory is that increased salt intake (consumption of salty snacks and processed foods) and insufficient fluid intake have led to increased urinary calcium and oxalate concentrations and stone formation. The increasing obesity epidemic is also paralleling increasing urolithiasis in children. Oral antibiotic use of certain classes at a younger age has also been associated with an increased risk for nephrolithiasis.

Bowen DK, Tasian GE. Pediatric stone disease. *Urol Clin North Am.* 2018;45(4):539–550.

Tasian GE, Jemielita T, Goldfarb D, et al. Oral antibiotic exposure and kidney stone disease. *J Am Soc Nephrol.* 2018;29(6):1731–1740.

169. What are the clinical findings in pediatric urolithiasis?

Patients present most commonly with flank pain, usually unilateral, with nausea and vomiting. One-half or more of children with abdominal or flank pain eventually diagnosed with urolithiasis will not have specific urinary symptoms, so a reasonable index of suspicion should be maintained. Although hematuria (>2 RBCs/HPF) is common, up to 15% may not have detectable hematuria. Most children will not have calculi revealed by ultrasound or plain x-ray ("occult urolithiasis"). In about one-third of cases, there is a family history of urolithiasis. Fever, dysuria, and costovertebral angle tenderness lower the likelihood of stones and make infection more likely, although both may occur together.

Marzuillo P, Guarino S, Apicella A, et al. Why we need a higher suspicion index of urolithiasis in children. *J Pediatr Urol.* 2017;13(2):164–171.

Persaud AC, Stevenson MD, McMahon DR, Christopher NC. Pediatric urolithiasis: clinical predictors in the emergency department. *Pediatrics.* 2009;124(3):888–894.

170. What is the composition of kidney stones in children?

Calcium (58%), struvite (25%), cysteine (6%), uric acid, urate (9%), and others (2%).

171. What is the most common cause of pediatric urinary calculi?

Idiopathic hypercalciuria is the most common cause of pediatric urinary calculi. Other causes include:

- Hypercalcemia
- Hypocitraturia
- Hyperoxaluria
- Cystinuria
- Renal tubular dysfunction (usually type 2 distal renal tubular acidosis [dRTA])
- Endocrine (hypothyroidism, adrenocorticoid excess, hyperparathyroidism)
- Bone metabolism disorders (immobilization, rickets, malignancies, juvenile rheumatoid arthritis)
- Drugs (loop diuretics, excess vitamin D, corticosteroids)
- UTI
- Polycystic kidneys (dominant and recessive)

A comprehensive metabolic evaluation is indicated in all children with calculi because of the high risk for recurrences in children with idiopathic hypercalciuria and hypocitraturia and the importance of excluding rare but treatable conditions such as primary hyperoxaluria and cystinuria.

Gouru VR, Pogula VR, Vaddi SP, et al. Metabolic evaluation of children with urolithiasis. *Urol Ann.* 2018;10(1):94–99.

Spivacow FR, Negri AL, del Valle EE, et al. Metabolic risk factors in children with kidney stone disease. *Pediatr Nephrol.* 2008;23:1129–1133.

172. How is hypercalciuria defined in pediatrics?

The strict definition of hypercalciuria in a child is **>4 mg of urinary calcium/kg per 24 hours** on a normal, unrestricted diet for the child's age. Random urine collections are used to screen for hypercalciuria. The **urine calcium-to-creatinine ratio** varies with age. Morning nonfasting urine ratios that exceed the following criteria correlate with quantitative hypercalciuria:

Age (years)	*Ratio*
>7	>0.24
5-7	>0.30
3-5	>0.41
1-2	>0.56
<1	>0.81

173. What are the appropriate laboratory studies for the initial evaluation of children with renal stones?

- Serum electrolytes, calcium, phosphorus, and creatinine
- Twenty-four-hour urine collection for sodium, calcium, creatinine, urate, citrate, uric acid, oxalate, and cystine
- Urine pH (by meter), UA, and urine culture (if indicated)
- Stone analysis on an available stone
- Serum PTH and vitamin D in patients with hypercalciuria, hypercalcemia, or hypophosphatemia

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Bevill M, Kattula A, Cooper CS, Storm DW. The modern metabolic stone evaluation in children. *Urology.* 2017;101:15–20.
Nicoletta JA, Lande MB. Medical evaluation and treatment of urolithiasis. *Pediatr Clin North Am.* 2006;53(3):479–491.

174. When is lithotripsy or surgery indicated for children with kidney stones?

Most stones up to 5 mm will pass spontaneously. Shock wave lithotripsy (SWL) is useful for children with pelvic or bladder stones that are radiopaque in whom fluoroscopy can be used to focus the shock waves. In general, SWL has a success rate of less than 50% with stones larger than 2 cm. Surgery (percutaneous nephrolithotomy) is reserved for stones causing urinary tract obstruction in children and for staghorn calculi in older patients. Cystine stones are difficult to fragment by SWL. Distal urethral stones are removed by ureteroscopy.

Miah T, Kamat D. Pediatric nephrolithiasis: a review. *Pediatr Ann.* 2017;46(6):e242–e244.
Mandeville JA, Nelson CP. Pediatric urolithiasis. *Curr Opin Urol.* 2009;19(4):419–423.

VESICOURETERAL REFLUX

175. How is primary VUR graded?

VUR, the retrograde flow of urine from the bladder into the upper urinary tract, is typically divided into five grades, as shown in Fig. 12.10. Secondary VUR (e.g., from posterior urethral valves) is not graded, but rather is described.

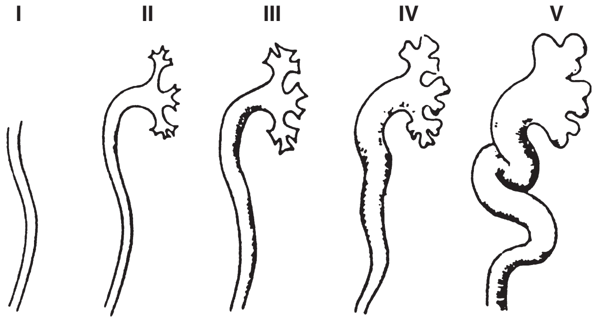

Fig. 12.10 The five grades of vesicoureteral reflux.

176. What is the natural history of VUR?

The likelihood that reflux will resolve spontaneously is influenced by the severity of the reflux at the time of the initial diagnosis. About 80% to 90% of patients with grade I to II reflux, 70% (<age 2 years) with grade III reflux, and 60% with unilateral grade IV reflux will experience spontaneous resolution within 5 years. Spontaneous resolution of grade V reflux is uncommon. The chances for resolution are better in younger children and those with unilateral—rather than bilateral—reflux, especially for the higher grades of reflux.

Elder JS, Peters CA, Arant BS Jr, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J Urol.* 1997;157(5):1846–1851.

177. How is VUR managed: medically or surgically?

This is controversial. There are significant institutional differences given differing opinions on the role of VUR as a predisposing factor to acute pyelonephritis, renal scarring, and CKD, as well as the value of prophylactic antibiotics.

- **Grades I to II**: These grades are usually managed medically, usually without prophylactic antibiotics, and have a higher likelihood of spontaneous resolution and a lower likelihood of significant sequelae.
- **Grades III to IV**: If followed expectantly, these types of reflux will resolve slowly, at a rate of about 10% per year. Surgical intervention at the ureterovesicular junction will result in the elimination of this degree of reflux in the vast majority of patients, but randomized studies have not shown any significant difference in long-term renal outcome (e.g., renal scarring, hypertension, reduced function) when comparing medical versus surgical treatment. Prophylactic antibiotics are commonly used for these grades.
- **Grade V:** Surgical intervention is typically indicated, particularly if the patient is older (>6 years) and significant renal scarring has been noted.

Edwards A, Peters CA. Managing vesicoureteral reflux in children: making sense of all the data. *F1000Res.* 2019;8:10.12688.
Martin AD, Iqbal MW, Sprague MD, et al. Most infants with dilating vesicoureteral reflux can be treated nonoperatively. *J Urol.* 2014;191(5 Suppl):1620–1626.
Peters CA, Skoog CJ, Arant BS Jr, et al. Summary of the American Urological Association guidelines on management of primary vesicoureteral reflux in children. *J Urol.* 2010;184(3):1134–1144.

178. Are antibiotics effective to prevent recurrent UTIs in children with reflux?

The effectiveness of antibiotics in the setting of significant reflux has been controversial and the results mixed. A 2014 well-designed Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial has found that treatment of children with VUR (grades I to IV) with a prophylactic antibiotic (trimethoprim-sulfamethoxazole) compared with placebo was associated with a substantially reduced risk for recurrent UTIs, but not of renal scarring for children treated after a first or second UTI. The authors have questioned whether this decrease in recurrences in the setting of reflux might spur a reevaluation of the AAP's recommendation to not routinely do a reflux imaging study after a first UTI.

Lee T, Park JM. Vesicoureteral reflux and continuous prophylactic antibiotics. *Investig Clin Urol.* 2017;58(Suppl 1):S32–S37.
RIVUR Trial Investigators, Hoberman A, Greenfield SP, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med.* 2014;370(25):2367–2376.

179. Should asymptomatic siblings of a patient with VUR have urologic imaging done as a screen for reflux?

Some studies have demonstrated reflux in 33% to 45% of siblings of patients with reflux. Among identical twins, the rate is 80%. Typically, the reflux is milder (grades I to II); only 2% of siblings in published studies have reflux of grades IV or V. Although the incidence of reflux is higher in siblings, data are still lacking that the screening and treatment of asymptomatic siblings decreases renal scarring.

Nelson CP, Finkelstein JA, Logvinenko T, Schuster MA. Incidence of urinary tract infection among siblings of children with vesicoureteral reflux. *Acad Pediatr.* 2016;16(5):489–495.
Routh JC, Grant FD, Kokorowski P, et al. Costs and consequences of universal sibling screening for vesicoureteral reflux: a decision analysis. *Pediatrics.* 2010;126:865–871.

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CHAPTER 13

NEUROLOGY

Tiffani L. McDonough, MD and James J. Riviello, Jr., MD

ANTIEPILEPTIC DRUGS

1. Should treatment with antiepileptic drugs (AEDs) be started after the first afebrile seizure in a child?

Children with an isolated, uncomplicated seizure usually do not require AED therapy. Epidemiologic studies have shown that about one-third to one-half of children with an uncomplicated single seizure, a normal neurologic examination, and normal electroencephalogram (EEG) will experience a second seizure. "Delaying" treatment until after the second seizure does not adversely affect the long-term chance of epilepsy remission. In fact, delaying treatment until 10 seizures may not affect remission, depending upon the underlying epilepsy syndrome.

Other factors, including EEG results, antecedent neurologic history, family history, and imaging (in selective cases), influence the risk for recurrence and should be considered. Identification of an epilepsy syndrome is particularly important. Risk for recurrent seizures is sharply increased if the seizure was nocturnal, the neurologic status is not normal, there is a positive family history, no immediate precipitating cause can be identified, and the EEG reveals epileptiform discharges. Not even status epilepticus as the initial seizure increases the overall risk for seizure recurrence, but it does increase the risk that the next seizure could be status epilepticus.

Sansevere AJ, Avalone J, Strauss LD, et al. Diagnostic and therapeutic management of a first unprovoked seizure in children and adolescents with a focus on the revised diagnostic criteria for epilepsy. *J Child Neurol.* 2017;32(8):774–778.

Rizvi S, Ladino LD, Hernandez-Ronquillo L, Téllez-Zenteno JF. Epidemiology of early stages of epilepsy: risk of seizure recurrence after a first seizure. *Seizure.* 2017;49:46–53.

Haut SR, Shinnar S. Considerations in the treatment of a first unprovoked seizure. *Semin Neurol.* 2008;28(3):289–296.

2. What is the advantage of monotherapy as opposed to polydrug therapy for epilepsy?

- Chronic toxicity is directly related to the number of drugs administered.
- As compared with monotherapy, intellectual and sensorium impairment is increased for any given AEDs (despite "normal" drug levels).
- Drug interactions may paradoxically lead to loss of seizure control.
- It is difficult to identify the cause of an adverse reaction.

Menkes JH, Sankar R. Paroxysmal disorders. In Menkes JH, Sarnat HB, Maria BL, eds. *Child Neurology.* 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:891–893.

3. Which AEDs are recommended for primary generalized tonic-clonic seizures in children over 1 month of age?

The "traditional" or "older" AEDs (phenobarbital, primidone, phenytoin) are no longer considered the drugs of choice for generalized convulsive seizures for many age groups because of adverse effects. Studies have shown that most of the major anticonvulsants have comparable efficacy for reducing or eliminating seizure recurrences.

Class I evidence demonstrates that topiramate, lamotrigine, levetiracetam, valproate, and zonisamide are effective for the treatment of primary generalized tonic-clonic seizures. Carbamazepine and oxcarbazepine may cause an increased frequency of primary generalized seizures, especially absence and myoclonic types, and are the drugs of choice for localization-related (focal) epilepsies. The choice of an AED is generally made on the dichotomy of seizure onset: either generalized onset or focal onset.

Note that phenobarbital remains the first-line drug of choice for neonatal seizures, although phenytoin has equal efficacy. Phenobarbital is absorbed well in the newborn; phenytoin is not.

Sankaraneni R, Lachhwani D, Antiepileptic drugs—a review. *Pediatr Ann.* 2015;44:e36–e42.

Rosati A, DeMasi S, Guerrini R. Antiepileptic drug treatment in children with epilepsy. *CNS Drugs.* 2015;29(10):847–863.

4. What is the drug of choice for absence epilepsy?

Ethosuximide (Zarontin), **valproate** (divalproex sodium or Depakote), and **lamotrigine** (Lamictal) are all effective for eliminating or substantially reducing the number of absence attacks. Ethosuximide is traditionally the drug of choice, for several reasons:

- It works well for many patients. It not only stops the clinical attacks of absence but it often normalizes the EEG by actually eliminating the 3Hz (3 per second) spike-wave discharges.

- It is well tolerated by most patients. Although rare cases of serious bone marrow, liver, or dermatologic disorders have occurred, routine or frequent blood tests are not considered obligatory by most physicians.
- It has a relatively long serum half-life (40 hours). Thus, once- or twice-daily dosing is appropriate and represents a real convenience to the patient.
- It is relatively inexpensive.

A disadvantage is that ethosuximide is primarily effective against absence seizures but not convulsive seizures. Children with coexisting generalized convulsions should be treated with valproate or lamotrigine. Disadvantages of valproate include risks for idiosyncratic liver toxicity, especially with an underlying metabolic disease, pancreatopathy, thrombocytopenia (dose and duration-related), low vitamin D levels, osteopenia, weight gain, and teratogenicity. Lamotrigine should also be considered. It has a generally favorable cognitive and endocrine profile but an increased risk for rash (risk increases with valproic acid).

Kessler SK, McGinnis E. A practical guide to treatment of childhood absence epilepsy. *Paediatr Drugs.* 2019;21(1):15–24.
Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med.* 2010;362:790–799.

5. Can AEDs paradoxically cause a worsening of seizures?

A paradoxical worsening of seizure control by various AEDs has been noted for decades. In fact, every AED may aggravate seizures in an individual patient. Mechanisms may include nonspecific effects of drug intoxication. In addition, specific medications may exacerbate specific seizure types, referred to as a *pharmacologic insensitivity.* For example, carbamazepine may worsen the absence, myoclonic, and astatic (atonic or drop) seizures seen in generalized epilepsy syndromes; phenytoin and vigabatrin may also worsen generalized seizures; and gabapentin and lamotrigine may worsen myoclonic seizures. The clinical trap to avoid is assuming that increasing seizures are related to the underlying epilepsy and that increasing doses are needed. With a paradoxical worsening, seizures will continue to worsen or not improve as the dose is increased. Ideally, the frequency of seizures should decrease as the dose of the AED is increased.

Gayatri NA, Livingston JH. Aggravation of epilepsy by anti-epileptic drugs. *Dev Med Child Neurol.* 2006;48(5):394–398.
Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia.* 1998;39:5–17.

6. How should serum AED levels be utilized?

Trough serum drug levels should be obtained to detect subtherapeutic or toxic concentrations. It is most helpful to check the serum level *right before the dose,* preferably in the morning before any medication is given. An **inadequate serum concentration** is the most common cause of persistent seizures, but **drug toxicity**, especially with phenytoin, may also manifest by deteriorating seizure control. There generally will be less variation in blood concentrations with tablets or capsules compared with liquid preparations; suspensions in particular result in notoriously inconsistent dosages. If drug toxicity is suspected, **peak** serum levels should be measured.

Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: a 2018 update. *Ther Drug Monit.* 2018;40(5):526–548.
Stepanova D, Beran RG. The benefits of antiepileptic drug (AED) blood level monitoring to complement clinical management of people with epilepsy. *Epilepsy Behav.* 2015;42:7–9.

7. What are the suggested therapeutic ranges of AEDs?

See Table 13.1.

Table 13.1 Drug/Trade Name Target Plasma Drug Concentration Range*

DRUG (GENERIC)	BRAND NAME	TARGET DRUG LEVEL
Carbamazepine	Tegretol/Carbatrol	4-12 mcg/mL
Clobazam	Onfi	Not done
Ethosuximide	Zarontin	40-100 μg/mL
Felbamate	Felbatol	30-100 μg/mL
Gabapentin	Neurontin	4-20 μg/mL
Lacosamide	Vimpat	5-10 μg/mL
Lamotrigine	Lamictal	2-20 mcg/mL
Levetiracetam	Keppra	10-60 μg/mL
Oxcarbazepine	Trileptal	10-40 μg/mL

Continued on following page

Table 13.1 Drug/Trade Name Target Plasma Drug Concentration Range (*Continued*)

DRUG (GENERIC)	BRAND NAME	TARGET DRUG LEVEL
Phenobarbital	Luminal	10-45 μg/mL
Phenytoin	Dilantin, Fosphenytoin	10-20 mcg/mL
Primidone	Mysoline	5-10 mg/mL
Rufinamide	Banzel	3-30 μg/mL
Tiagabine	Gabitril	20-200 ng/mL
Topiramate	Topamax	2-25 μg/mL
Valproate	Depakene/Depakote	50-100 mcg/mL
Vigabatrin	Sabril	Not done
Zonisamide	Zonegran	10-40 μg/mL

[*] Therapeutic ranges are just guidelines for dosing. Seizures may respond to a low level, and toxicity may occur at a low level. Levels above "normal" may be needed to control seizures and can be used if tolerated. It is important to treat the patient and not the "level."

8. What are the typical dose-related side effects of AEDs?

Dose-related side effects (adverse effects) occur somewhat predictably and can be anticipated, particularly as the medication dose is initiated and escalated. Dose-related side effects are referred to as *"nuisance"* side effects. Common dose-related side effects include sedation, headache, gastrointestinal irritation, unsteadiness, and dysarthria. Management commonly consists of reducing the dose by 25% to 50% and waiting about 2 weeks for tolerance to develop. In addition, behavioral and cognitive side effects can occur in some patients; these can be subtler, and controversy exists regarding the relative effects of various AEDs. Dose-related side effects should be contrasted with direct organ toxicity to the liver, pancreas, and bone marrow, which may result in significant morbidity and even mortality.

Moavero R, Pisani LR, Pisani F, Curatolo P. Safety and tolerability profile of new antiepileptic drug treatment in children with epilepsy. *Expert Opin Drug Saf.* 2018;17(10):1015–1028.

9. What idiosyncratic drug reactions are associated with antiepileptic medications?

Idiosyncratic reactions occur unpredictably, are potentially fatal, and do not correlate with dose of medication.

- **Carbamazepine:** leukopenia, aplastic anemia, thrombocytopenia, hepatic dysfunction, *rashes*
- **Ethosuximide:** leukopenia, pancytopenia, rashes
- **Phenobarbital:** rashes, Stevens-Johnson syndrome, hepatic dysfunction
- **Phenytoin:** hepatic dysfunction, lymphadenopathy, movement disorder, Stevens-Johnson syndrome, fulminant hepatic failure
- **Valproic acid:** fulminant hepatic failure (especially in at-risk patients, see question 10), hyperammonemia, pancreatitis, thrombocytopenia, rash, stupor
- **Lamotrigine:** Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic failure, DRESS syndrome (**D**rug **R**ash with **E**osinophilia and **S**ystemic **S**ymptoms), aseptic meningitis
- **Ezogabine:** blue discoloration of skin

10. Which children are most susceptible to valproic acid–induced acute hepatic failure?

The highest incidences occur in children **<2 years who are receiving polytherapy** (1 in 540). In children <2 years who are receiving valproic acid monotherapy, the rate is reduced to about 1 in 8000. The complication is unrelated to dosage and typically occurs during the first 3 months of therapy. Up to 40% of individuals who receive valproic acid will have dose-related elevations of liver enzymes that are transient or resolve with dosage adjustments. However, liver function test monitoring is not helpful for predicting acute hepatic failure. It has been hypothesized that valproic acid may cause carnitine deficiency, hyperammonemia, and hepatotoxicity. Despite a lack of data from clinical trials, some clinicians recommend prophylactic carnitine supplementation, especially in a high-risk patient.

Alpers syndrome is a rare, autosomal recessive neurometabolic disease, often presenting with intractable seizures and psychomotor regression. The disease is caused by a mutation in polymerase gamma (POLG), which encodes for a mitochondrial DNA polymerase. Children with Alpers syndrome are at increased risk for fulminant hepatic failure with valproic acid administration, and this agent should be used with caution if this condition is suspected.

Guo HL, Jing X, Sun JY, et al. Valproic acid and the liver injury in patients with epilepsy: an update. *Curr Pharm Des.* 2019;25(3):343–351.

Saneto RP, Lee IC, Koenig MK, et al. POLG DNA testing as an emerging standard of care before instituting valproic acid therapy for pediatric seizure disorders. *Seizure.* 2010;19(3):140–146.

11. What are the warning signs and symptoms of hypersensitivity syndromes to AEDs?

Symptoms often occur early, within the first months of treatment. Families need to be educated about the potential for drug reactions. Concerning symptoms include:

- Body temperature >104°F (40°C)
- Protracted vomiting
- Lethargy
- Exfoliation of the skin (palm or sole) or mucosal lesions, with bleeding
- Facial edema or swelling of the tongue
- Confluent erythema, palpable purpura
- Protracted bleeding from minor cuts
- Lymph node enlargement
- Wheezing (indicating anaphylaxis)

Multiple studies have shown that families fail to appreciate evolving symptoms of idiosyncratic reactions and continue to administer the offending agent. Laboratory abnormalities may include eosinophilia, atypical lymphocytosis, and abnormal liver function enzymes. Routine surveillance of blood chemistries and complete blood counts (every 3 to 6 months) are part of standard practice, but they are unlikely to identify potentially life-threatening conditions.

Ye YM, Thong BY, Park HS. Hypersensitivity to antiepileptic drugs. *Immunol Allergy Clin North Am.* 2014;34(3):633–643.

12. What is Diastat?

Diazepam rectal gel (Diastat) has been approved for the treatment of status epilepticus and severe recurrent convulsive seizures in children. It is prescribed for home use by parents as an emergency medication. Dosages (as they are for most medications in pediatric patients) are based on weight, and the medication is available in various premixed concentrations with syringe applicators. Parents are generally counseled to administer the medication for a seizure lasting greater than 5 minutes and to call 911 with administration because respiratory depression can occur with administration of benzodiazepines. There is no age limitation.

13. Are there other options for outpatient treatment of severe recurrent and prolonged seizures in children?

As of 2014, rectal diazepam is the only formulation approved in the United States by the Food and Drug Administration (FDA) for out-of-hospital treatment. Clinical trials are in progress for alternatives such as intranasal midazolam, diazepam and lorazepam, buccal midazolam (approved in the European Union), sublingual lorazepam, and intramuscular diazepam by autoinjection. Intranasal midazolam, with an atomizer or even dripped into the nares, is frequently used in clinical practice.

Maglalang PD, Rautiola D, Siegel RA, et al. Rescue therapies for seizure emergencies: new modes of administration. *Epilepsia.* 2018;59(Suppl 2):207–2015.

14. After what period can AEDs be safely discontinued?

The withdrawal of AEDs should be considered when the child is free of seizures for 2 years, because well-controlled investigations have shown that the risk for relapse in children whose seizures have been in remission for 2 years is low. A 4-year period of seizure freedom was the previous standard. Some have used a 1-year seizure-free period. Although there is no uniform agreement about factors that are predictive of outcome, the highest remission rate appears to occur in those who are otherwise neurologically normal and in whom the EEG at the time of discontinuation lacks specific epileptiform features and displays a normal background. The prognosis is the worst for children with symptomatic epilepsies, persistently abnormal EEGs, and abnormal neurologic examinations. Remission also depends upon the underlying epilepsy syndrome.

Schmidt D, Sillanpää M. Stopping epilepsy treatment in seizure remission: good or bad or both? *Seizure.* 2017;44:157–161.
Braun KP, Schmidt D. Stopping antiepileptic drugs in seizure-free patients. *Curr Opin Neurol.* 2014;27(2):219–226.

15. When the decision is made to discontinue AEDs, how should tapering be done?

In practice, all AEDs should be tapered gradually rather than abruptly discontinued, although there is no actual withdrawal state produced by a "cold turkey" reduction of most AEDs (e.g., phenytoin, carbamazepine, valproate, ethosuximide). By contrast, a withdrawal syndrome of agitation, signs of autonomic overactivity, and seizures follows the sudden elimination of habitually consumed benzodiazepines (diazepam, clonazepam, clobazam, lorazepam) or short-acting barbiturates (e.g., secobarbital). The long elimination half-life of phenobarbital lessens the risk for withdrawal symptoms after abrupt discontinuation.

In a study of more than 100 children who had been seizure free for either 2 or 4 years, the risk for seizure recurrence during tapering and after discontinuation of the AED was no different if the period of taper was 6 weeks or 9 months. Rapid tapering appears to be an acceptable means of discontinuation. If a patient has been on polytherapy, some experts may rapidly taper some of the AEDs, but more slowly taper the last AED.

Stagi S Lasorella S, Piccorossi A, et al. Cessation of epilepsy therapy in children. *Expert Rev Neurother.* 2016;6(5):549–559.
Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. *Cochrane Database Syst Rev.* 2006;19(2):CD005003.
Tennison M, Greenwood R, Lewis D, Thorn M. Discontinuing antiepileptic drugs in children with epilepsy: a comparison of a six-week and a nine-month taper period. *N Engl J Med.* 1994;330(20):1407–1410.

CEREBRAL PALSY

16. What is cerebral palsy?

Cerebral palsy (CP) describes a *heterogeneous* group of nonprogressive (static) motor and posture disorders of cerebral or cerebellar origin that typically manifest early in life. The primary impairment involves *significant deficits in motor planning and control.* Nonprogressive, clinical manifestations often change over time as the functional expression of the underlying brain is modified by brain development and maturation. However, motor function that is affected results from the part of the brain that is injured. Causes include cerebral malformations, metabolic and genetic causes, infection (both intrauterine and extrauterine), stroke, hypoxia-ischemia, and trauma. It should be noted that nonprogressive refers to the neuropathology and not the examination; tone and posture may change over time in a static process.

Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. *Lancet.* 2014;383(9924):1240–1249.
United Cerebral Palsy Association. www.ucp.org. Accessed January 22, 2020.

17. What are the most common brain lesions seen on magnetic resonance imaging (MRI) in children with CP?

Periventricular white matter lesions are the most common abnormalities and can be seen in 19% to 45% of children with CP (particularly formerly premature infants). Other common lesions include gray matter injuries of the basal ganglia and thalamus (21%), developmental cortical malformations (11%), and focal cortical infarcts (10%). Up to 15% of cases of CP do not have an identifiable lesion on MRI. The varied MRI findings are believed to be emblematic of the neurodevelopmental heterogeneity of CP.

Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. *JAMA Pediatr.* 2017;171(9):897–907.

18. What are the Levine (POSTER) criteria for the diagnosis of CP?

- **P**osturing/abnormal movements
- **O**ropharyngeal problems (e.g., tongue thrusts, swallowing abnormalities)
- **S**trabismus
- **T**one (hypertonia or hypotonia)
- **E**volutional maldevelopment (primitive reflexes persist or protective/equilibrium reflexes fail to develop [e.g., lateral prop, parachute reflex])
- **R**eflexes (increased deep tendon reflexes/persistent Babinski reflex)
- Abnormalities in four of these six categories strongly point to the diagnosis of CP.

Feldman HM. Developmental-behavioral pediatrics. In Zitelli BJ, Davis HW, eds. *Atlas of Pediatric Diagnosis.* 5th ed. St. Louis, MO: Mosby; 2007:82.

19. What are the types of CP?

Clinical classification is based on the nature of the movement disorder and muscle tone and anatomic distribution. A single patient may have more than one type. Spastic CP is the most common, accounting for about two-thirds of cases.

- **Spastic (or pyramidal) CP:** Characterized by neurologic signs of upper motor neuron damage with increased “clasp knife” muscle tone, increased deep tendon reflexes, pathologic reflexes, and spastic weakness. Spastic CP is subclassified based on distribution:
  - *Hemiplegia*: Primarily unilateral involvement, arm usually more than leg
  - *Quadriplegia*: All limbs involved, with legs often more involved than arms
  - *Diplegia*: Legs much more involved than arms, which may show no or only minimal impairment (more common in the premature infant)
- **Dyskinetic (nonspastic or extrapyramidal) CP:** Characterized by prominent involuntary movements or fluctuating muscle tone, with choreoathetosis the most common subtype. Distribution is usually symmetric among the four limbs.
- **Ataxic CP:** Primarily cerebellar signs (including ataxia, dysmetria, past pointing, nystagmus)
- **Mixed types:** Features of multiple types of cerebral palsy

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Richards CL, Malouin F. Cerebral palsy: definition, assessment and rehabilitation. *Handb Clin Neurol.* 2013;111:183–195.

20. What proportion of CP is related to birth asphyxia?

In contrast with popular perception, large clinical epidemiologic and longitudinal studies indicate that perinatal asphyxia is an important—but relatively minor—cause. Estimates range from a low of 3% to a high of 21%. In most cases, the events leading to CP occur in the fetus before the onset of labor or in the newborn after delivery.

Pappas A, Korzeniewski SJ. Long-term cognitive outcomes of birth asphyxia and the contribution of identified perinatal asphyxia to cerebral palsy. *Clin Perinatol.* 2016;43(3):559–572.

McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol.* 2013;122(4):869–877.

21. How well do Apgar scores correlate with the development of CP?

Large studies have mixed results. A 1981 study of 49,000 infants found that a low Apgar score correlated poorly with the development of CP. Of term infants with scores of 0 to 3 at 1 or 5 minutes, 95% did not develop CP. Conversely, nearly 75% of patients with CP had 5-minute Apgar scores of 7 to 10. More recent studies have found a stronger association between low Apgar scores and CP in term infants, but there is no clear association with low birth weight or premature infants. A 2010 population study of over 500,000 Norwegian infants found an association between an Apgar score <4 at 5 minutes and CP, which was strongest for infants with normal birth weight and for patients later diagnosed with quadriplegia. A 2018 study in Sweden of over 1.2 million newborns found risks of CP inversely associated with 5- and 10-minute Apgar scores.

Persson M, Razaz N, Tedroff K, et al. Five and 10 minute Apgar scores and risks of cerebral palsy and epilepsy: population based cohort study in Sweden. *BMJ.* 2018;360:k2017.

Lie KK, Groholt E-K, Eskild A. Association of cerebral palsy with Apgar score in low and normal birthweight infants: population based cohort study. *BMJ.* 2010:341:c4990.

Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. *Pediatrics.* 1981;68:36–44.

22. Why is CP difficult to diagnose clinically during the first year of life?

Unlike adults with acute neurologic deficits, which may be focal, young children may manifest generalized and nonspecific neurologic dysfunction after an acute neurologic insult:

- Hypotonia is more common than hypertonia in the first year after an acute insult, and spasticity typically develops later, both of which make the prediction of CP difficult. Hypertonia, especially in the antigravity muscles, develops to compensate for weakness. Initial hypertonia may be seen with a basal ganglia insult.
- The early abundance of primitive reflexes (with variable persistence) may confuse the clinical picture.
- An infant has a limited variety of volitional movements for evaluation.
- Substantial myelination takes months to evolve and may delay the clinical picture of abnormal tone and increased deep tendon reflexes.
- Most infants who develop CP do not have identifiable risk factors; most cases are not related to labor and delivery events (intrapartum).
- The examination may also improve over time as the child develops.
- Most cases of CP can be diagnosed by 18 to 24 months of life.

Morgan C, Fahey M, Roy B, Novak I. Diagnosing cerebral palsy in full-term infants. *J Paediatr Child Health.* 2018;54(10):1159–1164.

Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. *JAMA Pediatr.* 2017;171(9):897–907.

Shapiro BK, Capute AJ. Cerebral palsy. In McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB, eds. *Oski's Pediatrics, Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:1910–1917.

KEY POINTS: CEREBRAL PALSY

1. Apgar scores correlate relatively poorly with the ultimate diagnosis of CP.
2. During the first year of life, hypotonia is more common than hypertonia in patients who are ultimately diagnosed with the disease.
3. Keep an eye on the eyes: As many as 75% of children with CP have ophthalmologic problems (e.g., strabismus, refractive errors).
4. Spastic hemiplegia is the most common type of CP that is associated with seizures.
5. Monitor regularly for hip subluxation, especially in patients with spastic diparesis, because earlier identification assists therapy.

23. What behavioral symptoms during the first year should arouse suspicion about the possibility of CP?

- Excessive irritability, constant crying, and sleeping difficulties (severe colic is noted in up to 30% of babies who are eventually diagnosed with CP)

- Early feeding difficulties, with difficulties in coordinating suck and swallow, frequent spitting up, and poor weight gain
- "Jittery" or "jumpy" behavior, especially at times other than when hungry
- Easily startled behavior
- Stiffness when handled, especially during dressing, diapering, and handwashing
- Paradoxically "precocious" development, such as early rolling (actually a sudden, reflexive roll rather than a volitional one), or apparent early strength, such as the stiff-legged "standing" with support of an infant with spastic diplegia

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Spittle AJ, Morgan C, Olsen JE, et al. Early diagnosis and treatment of cerebral palsy in children with a history of preterm birth. *Clin Perinatol.* 2018;45(3):409–420.
Bennett FC. Diagnosing cerebral palsy—the earlier the better. *Contemp Pediatr.* 1999;16:65–76.

24. What gross motor delays are diagnostically important in the infant with possible CP?

- Inability to bring the hands together in midline while in a supine position by the age of 4 months
- Head lag persisting beyond 6 months
- No volitional rolling by 6 months
- Inability to independently sit straight by 8 months
- No hands-and-knees crawling by 12 months

Spittle AJ, Morgan C, Olsen JE, et al. Early diagnosis and treatment of cerebral palsy in children with a history of preterm birth. *Clin Perinatol.* 2018;45(3):409–420.
Bennett FC. Diagnosing cerebral palsy—the earlier the better. *Contemp Pediatr.* 1999;16:65–76.

25. What problems are commonly associated with CP?

- **Intellectual disability:** Two-thirds of total patients; most commonly observed in children with spastic quadriplegia
- **Failure to thrive, growth retardation**
- **Feeding problems** (including dysphagia, sialorrhea [excessive salivation])
- **Gastrointestinal problems** (gastroesophageal reflux, constipation)
- **Learning disabilities**
- **Ophthalmologic abnormalities** (strabismus, amblyopia, nystagmus, refractive errors)
- **Hearing deficits**
- **Communication disorders**
- **Epilepsy:** One-half of total patients; most commonly observed in children with spastic hemiplegia and related to the degree of neuroimaging abnormality.
- **Behavioral and emotional problems** (especially attention-deficit/hyperactivity disorder, depression, sleep problems)
- **Urinary problems** (incontinence, voiding dysfunction, urinary tract infections)
- **Spinal column changes** (kyphosis, scoliosis)
- **Respiratory problems** (upper airway obstruction, chronic aspiration)

Sewell MD, Eastwood DM, Wimalasundera N. Managing common symptoms of cerebral palsy in children. *BMJ.* 2014;349:g4596.
Dodge NN. Cerebral palsy: medical aspects. *Pediatr Clin North Am.* 2008;55(5):1189–1207.

26. What features in an infant suggest a progressive central nervous system (CNS) disorder rather than CP as the cause of a motor deficit?

- **Abnormally increasing head circumference:** Possible hydrocephalus, tumor, or neurodegenerative disorder
- **Acquired microcephaly:** Metabolic disease or Rett syndrome
- **Eye anomalies:** Cataracts, retinal pigmentary degeneration, optic atrophy (possible neurodegenerative disease), coloboma, chorioretinal lacuna, optic nerve hypoplasia (possible Aicardi syndrome or septo-optic dysplasia)
- **Skin abnormalities:** Vitiligo, café au lait spots, nevus flammeus, port wine stain (possible Sturge-Weber syndrome or neurofibromatosis)
- **Hepatomegaly and/or splenomegaly** (possible metabolic or lysosomal storage disease)
- **Decreased or absent deep tendon reflexes** (possible peripheral neuropathy or mitochondrial disorder)
- **Sensory abnormalities:** Diminished sense of pain, position, vibration, or light touch
- **Developmental regression or failure to progress:** Rett syndrome or Leigh disease

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Taft LT. Cerebral palsy. *Pediatr Rev.* 1995;16(11):411–418.

27. What therapies are used to treat the spasticity and dystonia of CP?

- **Casting:** Serial "inhibitive" casting can reduce tone and allow improved gait and weight-bearing activities
- **Nerve blocks, motor point blocks, botulinum toxin:** Injected to target spasticity in particular muscle groups
- **Oral and intrathecal medications:** Including baclofen, dantrolene, carbidopa-levodopa, and clonazepam. Clonazepam may be helpful with concomitant epilepsy.
- **Tendon-lengthening surgeries:** At ankle, knee, wrist, or elbow to prevent or delay joint contractures
- **Selective dorsal rhizotomy:** A neurosurgical procedure that interrupts the afferent component of the deep tendon (stretch) reflex

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Nahm NJ, Graham HK, Gormley ME Jr, Georgiadis AG. Management of hypertonia in cerebral palsy. *Curr Opin Pediatr.* 2018;30(1):57–64.

CEREBROSPINAL FLUID

28. What is normal cerebrospinal fluid (CSF) pressure?

CSF pressure as measured during a lumbar puncture (LP) varies with age, positional technique, and combativeness of the patient. For truly accurate pressures, the child should be relaxed with legs extended. CSF can be seen in the manometer varying with respirations when the needle has been properly placed. As a general guide, the normal ranges of CSF opening pressures are:

- *Neonate:* 80 to 100 mm H_2O
- *1 month to 4 years:* 10 to 100 mm H_2O
- *8 years to adolescent/adult:* 100 to 200 mm H_2O
- *Adolescent to adult:* 100 to 250 mm H_2O (may reach 280 in obese or sedated patients) Any opening pressure $>$250 mm H_2O should be considered suspicious for intracranial hypertension.

Evidence exists that in the obese or sedated patient, a cutoff of 280 mm H_2O may be considered the upper limit of normal. Both elevated body mass index (BMI) and deep sedation may increase the opening pressure.

Avery RA. Interpretation of lumbar puncture opening pressure measurements in children. *J Neuroophthalmol.* 2014;34(3):284–287.

Ellis R 3rd. Lumbar cerebrospinal fluid opening pressure measured in flexed lateral decubitus position in children. *Pediatrics.* 2003;93(4):622–623.

29. What are the normal CSF volumes in an infant, child, and adolescent?

Estimates for the volume of the ventricular system are:

- 40 to 50 mL in a term newborn
- 65 to 100 mL in an older child
- 90 to 150 mL in a teenager or adult

The choroid plexus actively secretes a distillate of CSF at a rate of 0.3 to 0.4 mL per minute in children and adults, which equals about 20 mL per hour or 500 mL per day. This equates to an hourly CSF volume turnover rate of about 15%.

30. What are the common causes of an elevated CSF protein?

Elevated CSF protein (generally $>$30 mg/dL outside of the neonatal period) is a nonspecific finding that is encountered in various neurologic disorders. Several common etiologies should be considered:

- **Infection:** Tuberculous meningitis, acute bacterial meningitis (pneumococcal, meningococcal, *Haemophilus influenzae*), syphilitic or viral meningitis, encephalitis
- **Inflammation:** Guillain-Barré syndrome (GBS), multiple sclerosis, peripheral neuropathy, postinfectious encephalopathy
- **Tumor** of the cerebral hemispheres or spinal cord; a CSF block may cause a very elevated CSF protein
- **Vascular accidents**, such as cerebral hemorrhage (including subarachnoid hemorrhage, subdural hemorrhage, intracerebral hemorrhages) or stroke as a result of cranial arteritis, diabetes mellitus, or hypertension
- **Degenerative disorders** involving white-matter disease (e.g., Krabbe disease)
- **Metabolic disorders** (e.g., uremia)
- **Toxins** (e.g., lead)
- **Prematurity**, related to immaturity of the blood–brain barrier

31. What CSF findings suggest metabolic disease as a cause of neurologic signs and symptoms?

- **Elevated CSF protein concentration** is characteristic of metachromatic leukodystrophy, globoid cell encephalopathy, and some mitochondrial disorders.
- **Low CSF glucose concentration** is consistent with hypoglycemia caused by a defect of gluconeogenesis or a defect in the transport of glucose across the blood–brain barrier (GLUT-1 deficiency syndrome).
- **Low CSF folate concentration** suggests a defect involving folate metabolism.
- **Presence in the CSF of amino acids, specifically glycine, glutamate, and γ-aminobutyric acid (GABA)**, may be diagnostic of nonketotic hyperglycinemia, pyridoxine-dependent epilepsy, or another defect in GABA metabolism.

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Pediatrics & Neonatology Journals [Ahmed Manfy] on TELEGRAM

- **Lactate** and **pyruvate** values are elevated in CSF disorders of cerebral energy metabolism, including pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, numerous disturbances of the respiratory chain, and Menkes syndrome. Lactate elevations may be more meaningful than pyruvate.
- **Low CSF lactate** value may be seen in the GLUT-1 deficiency syndrome.
- **Abnormal CSF biogenic amines** suggest several disorders that are associated with disturbed neurotransmission.

32. Why is a stylet used during an LP?

A *stylet* is typically used during an LP to prevent epidermis (which might lodge in an open-ended needle) from being introduced into the subarachnoid space, where an epidermal tumor might form. There is debate about whether the stylet should be kept in place after the needle passes the subcutaneous space or removed at that point to allow a better assessment of CSF flow when the needle enters the subarachnoid space. After fluid has been collected, some experts advocate reinserting the stylet to prevent attached arachnoid strands from causing CSF leakage through the dura, which may cause prolonged headaches. In newborns, it has been more common to not use a stylet, although this practice should be avoided.

Schulga P, Grattan R, Napier C, Babiker MO. How to use…lumbar puncture in children. *Arch Dis Child Educ Pract Ed.* 2015;100 (5):264–271.

33. What is the difference between traumatic and atraumatic needles used in LPs?

The needles are distinguished by their tip configuration. *Traumatic* (or conventional) needles (the more commonly used) have beveled tips, which are designed to puncture through tissue with the opening at the tip to facilitate CSF collection. *Atraumatic* needles have blunt tips, much like pencil-point tips, with a side port for collection of fluid. In theory, atraumatic needles separate, rather than tear, dural fibers on insertion. This should result in less persistent fluid leak, which is thought to contribute to post-LP headaches. Several studies have demonstrated that the use of atraumatic needles lessens the likelihood of postprocedure headache.

Nath S, Koziarz A, Badhiwala JH, et al. Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. *Lancet.* 2018;391(10126):1197–1204.

34. What are the two classic signs of meningeal irritation?

- **Kernig sign**, or the straight-leg-raising sign, consists of flexing the hip to 90 degrees and attempting to extend the knee. The limitation of knee extension as a result of painful resistance is a positive sign.
- **Brudzinski sign** is a positive sign, and it is present if a reflex flexion of the thighs occurs when a patient's neck is passively flexed.

It should be noted that these signs may not be present in the infant or young child (<18 to 24 months) or a comatose patient.

35. How do the manifestations of increased intracranial pressure (ICP) differ in an infant compared with an older child?

- *Infant:* Increasing head circumference, delayed closure of the fontanel, suture separation, bulging fontanel, failure to thrive, macrocephaly, paresis of upward gaze (known as *setting-sun sign*), and high-pitched, shrill cry
- *Older child:* Headache (especially in the early morning, awakening the child from sleep, or association with vomiting), nausea, persistent vomiting, personality and mood changes, lethargy, anorexia, fatigue, somnolence, diplopia as a result of sixth-nerve palsy or third-nerve palsy with uncal herniation, papilledema (Fig. 13.1)

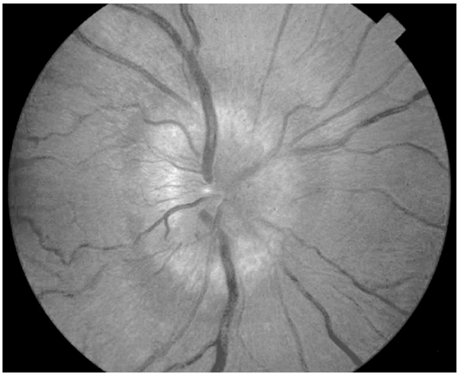

Fig. 13.1 Papilledema. Signs include swelling of the optic disc with blurring of normally sharp margins, venous engorgement, and curvature of blood vessels due to elevation of the disc. (From Douglas G, Nicol F, Robertson C, eds. *MacLeod's Clinical Examination*. 13th ed. London: Elsevier; 2013:285.)

36. What comprises the Cushing triad?

The *Cushing triad* consists of the development of **slow or irregular respirations, decreased heart rate**, and **elevated blood pressure** (particularly an increased systolic pressure with a widening pulse pressure) resulting from an increase in ICP. The Cushing triad may be observed in children with increased ICP or compression of the posterior fossa, which houses the medullary circulatory control center. It is a very late finding of increased ICP.

37. How is hydrocephalus classified?

Hydrocephalus refers to an increase in the CSF in the cerebral ventricles.

- **Communicating hydrocephalus** is caused by an inability to normally reabsorb CSF by the arachnoid granulations, which can occur from meningeal scarring as a result of bacterial meningitis, intraventricular hemorrhage, or intrathecal chemotherapy. It can be diagnosed if a tracer dye injected into one lateral ventricle appears in the lumbar CSF.
- **Noncommunicating hydrocephalus, or obstructed hydrocephalus**, refers to conditions causing intraventricular obstruction and alteration of the flow of dye into the lumbar CSF. Congenital malformations (especially aqueductal stenosis and Dandy-Walker syndrome with cystic dilation of the fourth ventricle) and mass lesions (e.g., tumors, arteriovenous malformations) can cause noncommunicating hydrocephalus. Obstructed hydrocephalus is frequently treated with a ventriculoperitoneal shunt. These shunts may now have pressure devices to avoid overdrainage (slit-ventricle syndrome).
- **Hydrocephalus ex vacuo** describes increases in CSF volume without increased CSF pressure, which is seen in conditions of reduced cerebral tissue (e.g., malformation, atrophy).

38. What is the normal growth rate of head circumference during the first year of life?

Head circumference at birth is about 34 to 35 cm for the term infant. The head circumference normally grows by 2 cm per month for the first 3 months of life, 1 cm per month for months 4 to 6, and 0.5 cm per month up to 1 year of life. The measurement of head circumference should be part of the examination of any child and should be plotted at every visit. The head circumference represents brain growth, but it is also influenced by hydrocephalus and subdural or epidural fluid collections.

39. What are the complications of ventricular shunts?

Ventricular shunts drain CSF from the ventricles in patients whose normal outflow or absorption has been blocked. The fluid may be drained to a variety of different locations, including the peritoneum, kidney, or cardiac atrium. Shunts draining CSF have remarkably improved the outcome of children with hydrocephalus, but they are subject to obstruction, infection, or mechanical malfunction. Shunt malfunctions present with signs of increased ICP. Children with shunt infections may have a low-grade fever, as well as signs of increased ICP. Because it is impossible to know the compliance properties of the ventricular system, children with shunt malfunction or infection are at risk for sudden, catastrophic decompensation. Children suspected of having shunt malfunctions or infection require urgent attention, and they should be closely observed until the shunt has been fully evaluated.

Boyle TP, Kimia AA, Nigrovic LE. Validating a clinical predication rule for ventricular shunt malfunction. *Pediatr Emerg Care.* 2018;34(11):751–756.

40. What are the characteristic features of idiopathic intracranial hypertension?

Idiopathic intracranial hypertension consists of increased ICP in the absence of a demonstrable mass lesion and with a normal CSF composition. The condition was formerly called *pseudotumor cerebri* or *benign intracranial hypertension.* The term *benign* has been de-emphasized because the problem has the potential to cause significant visual loss and to disrupt normal activities of daily living. Characteristic features include the following:

- Headache, fatigue, vomiting, anorexia, stiff neck, and diplopia from increased ICP.
- Normal neurologic examination except for papilledema or a third- or sixth-nerve palsy.
- Visual field constriction (usually nasal field) and enlargement of the blind spot on confrontational testing.
- Normal computed tomography (CT) scan. However, sometimes the ventricles are small.
- Normal CSF profile with the exception of an elevated opening pressure >250 mm H_2O
- MRI shows flattening of the posterior parts of the globes, empty sella, and narrowing of venous sinuses.

Sheldon CA, Paley GL, Beres SJ, et al. Pediatric pseudotumor cerebri syndrome: diagnosis, classification, and underlying pathophysiology. *Semin Pediatr Neurol.* 2017;24(2):110–115.

Glatstein MM, Oren A, Amarilyio G, et al. Clinical characterization of idiopathic intracranial hypertension in children presenting to the emergency department: the experience of a large tertiary care pediatric hospital. *Pediatr Emerg Care.* 2015;31(1):6–9.

Krishnakumar D, Pickard JD, Czosnyka Z, et al. Idiopathic intracranial hypertension in childhood: pitfalls in diagnosis. *Dev Med Child Neurol.* 2014;56(8):749–755.

41. What causes idiopathic intracranial hypertension?

Although there are multiple possible causes, more than 90% of cases are idiopathic. Among the reported causes are the following:

- **Drugs:** tetracycline, nalidixic acid, nitrofurantoin, corticosteroids, excess vitamin A (polar bear liver)

- **Endocrine disorders:** obesity, hyperthyroidism, Cushing syndrome, hypoparathyroidism
- **Thrombosis** of the dural venous sinuses as a result of head trauma, otitis media, mastoiditis, or obstruction of jugular veins in the superior vena cava syndrome

42. What treatment is recommended for severe cases of idiopathic intracranial hypertension?

Patients with sustained visual field loss or severe refractory headache are candidates for treatment. Specific treatment depends on the presence of an identifiable precipitant, which should be removed when possible. For example, the cessation of the offending medication (e.g., tetracycline) or weight reduction in obese patients is recommended. Nonspecific treatment includes the administration of acetazolamide, furosemide, or hydrochlorothiazide and, sometimes, corticosteroids. In severe cases, surgical intervention is available through installation of a lumboperitoneal shunt, optic nerve sheath decompression, or cranioplasty.

Jordan CO, Aylward SC. Intracranial hypertension: a current review. *Curr Opin Pediatr.* 2018;30(6):764–774.

CLINICAL ISSUES

43. What are the key questions in a neurologic evaluation?

- **Localization** of the lesion (Where is the lesion?)
- **Identification** of the lesion (What is the lesion?)
- **Time course** of the disorder (Is it paroxysmal [intermittent], acute, subacute, or chronic?)
- Presence of any **regression** (Is there a loss of previously learned skills?)
- **Development** of the nervous system (Is it age appropriate?)

44. What are general rules that govern localization of a potential neurologic problem?

Localization starts with the neurologic examination. The questions that need to be addressed are (1) is the examination normal or abnormal, and if abnormal, (2) is the abnormality focal, multifocal, or diffuse.

A problem can occur anywhere along the neuraxis: cerebrum, cerebellum, brainstem, spinal cord, nerve, neuromuscular junction, muscle, and even connective tissue.

- **Cerebrum:** may present with seizures, mental status changes, headaches, unilateral signs (such as hemiparesis)
- **Cerebellum:** may involve ataxia, disturbances of speech, disorders of limb movement, nystagmus
- **Brainstem:** combination of cranial nerve abnormalities and long-tract signs (symmetric weakness with or without sensory changes)
- **Spinal cord:** defined level of impairment with motor and/or sensory changes below involved area and normal examination above
- **Neuropathy:** distal more than proximal weakness with or without sensory changes
- **Muscle disease:** proximal more than distal weakness with decreased deep tendon reflexes and normal sensation
- **Connective tissue:** hypotonia without weakness

Goldstein JL. Pediatric neurology in the emergency department: localization followed by differential diagnosis. *Clin Pediatr Emerg Med.* 2008;9(2):87.

45. What distinguishes the pediatric neurologic examination?

Observation. The most useful information is often acquired by *watching the child move and play*. The level of interaction, creativity, and degree of sustained attention can be observed and are all important components of the mental status examination. By observing eye movements, response to sounds, the child's reaction to visual stimuli introduced into the peripheral visual field, and the symmetry of facial movements, most of the cranial nerves can be tested. Persistent asymmetries of spontaneous motor activity (e.g., consistently reaching across midline for an object) are reliable signs of weakness. Inspection of the seated posture and gait of the child provides an assessment of the cerebellum and cerebellar outflow pathways.

46. What are the advantages and disadvantages of various imaging procedures used in pediatric neurologic evaluation?

- **Skull x-ray films** are useful for detection of fractures, lytic lesions, and widened sutures. They have poor sensitivity and specificity for intracranial pathology in the setting of trauma.
- **CT scan without contrast** is the best imaging technique for neurologic emergencies to screen a patient with significant head trauma for skull fractures, signs of herniation, or acute intracranial hemorrhage. It can also be used to screen for acute strokes and subarachnoid hemorrhages. Midline or ventricular shifts due to masses and cerebral edema or increased ICP can be noted. The CT identifies bone clearly. This rapidly obtained study allows routine monitoring and is less expensive than MRI. There is a small risk associated with radiation from CT scans individually, but a known risk for malignancy with cumulative radiation doses. A CT scan generally excludes an acute neurosurgical emergency.

- **CT scan with contrast** uses radiodense contrast material to allow better identification of disruptions in the blood–brain barrier or of highly vascular structures, significantly improving detection of tumors, edema, focal inflammation, hemangiomas, and arteriovenous malformations.
- **MRI without contrast** is the preferred modality for most nonurgent examinations. It defines structures of brain more precisely than CT, especially within the spinal cord, posterior fossa, and cisterns. It is more effective for subtle hemorrhages (especially subacute and chronic) and for tumors or masses. MRI is now done for stroke, using a limited sequence study with diffusion weighted imaging. This can be rapidly performed. Different tissue-specific relaxation constants, called *T1* and *T2,* and proton density allow for better definition of white and gray matter. It also provides an image in three dimensions. Its longer testing time may require sedation. Furthermore, monitoring patients is more difficult in closed units. There are no known biologic hazards from MRI. MRI is contraindicated in patients with metallic implants that are ferromagnetic; this may heat and damage tissue.
- **MRI with contrast** is helpful in defining brain metastases and distinguishing postoperative scarring from other pathology.
- **Magnetic resonance angiography (MRA)** is a special type of MRI that displays larger arteries and veins without the use of contrast. It is less invasive than traditional arteriograms, and it is useful in defining arterial stenosis and identifying intracranial hemangiomas, arteriovenous malformations, and vascular aneurysms.
- **Magnetic resonance spectroscopy (MRS)** allows for in vivo examination of some chemical constituents of the brain, including N-acetylaspartate (NAA), a neuronal marker; choline; creatine; and lactate (a marker of energy metabolism).
- **Functional MRI (fMRI)** allows for in vivo anatomic localization of the motor and sensory cortex, the visual cortex, and components of expressive and receptive language.
- **Positron emission tomography (PET)** detects localized functional abnormalities using short half-life isotopes of carbon, nitrogen, oxygen, and fluorine. Labeled glucose ligands are useful in the evaluation of epileptic foci before surgery. These ligands identify areas of reduced cerebral glucose metabolism during interictal periods. Evaluation of specific isotopes, such as the uptake value of alpha-[11C] methyl-L-tryptophan (AMT) for the epileptic tuber in tuberous sclerosis, may be beneficial in certain disorders.
- **Single-photon emission computed tomography (SPECT)** uses gamma-ray emission of lipophilic isotopes in the measurement of cerebral blood flow and is also used in the study of refractory epilepsies.
- **Magnetoencephalography (MEG)** provides real-time measures of neuronal electrical activity (localization of epileptic focus).

Van Der Naalt J. Resting functional imaging tools (MRS, SPECT, PET and PCT). *Handb Clin Neurol.* 2015;127:295–308.

Menkes JH, Moser FG, Maria BL. Neurologic examination of the child and infant. In Menkes JH, Sarnat HB, Maria BL, eds. *Child Neurology.* 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:18–27.

47. A child presents with progressive left leg weakness and diplopia, especially when looking toward the left. Where is the lesion?

The described history, in combination with an examination showing upper motor neuron nerve dysfunction, long-tract signs, brisk reflexes, upgoing toe (Babinski sign), and a contralateral third-nerve palsy (down and out), localizes the lesion to the **right pyramidal tract before the decussation** (crossing over) and involves a lesion of the **right third-nerve nucleus**. The progressive course suggests a slow-growing lesion, such as a pontine glioma.

48. A dilated and unreactive pupil indicates the compression of what structure?

Third cranial nerve. This may be the result of compression anywhere along the course of the nerve. Uncal herniation is a medial displacement of the uncus of the temporal lobe and may cause this sign.

49. Pinpoint pupils and respiratory changes indicate the compression of what structure?

Progressive central herniation of the brain downward through the foramen magnum causes compression of the **pons** and can produce this finding.

50. How does the presentation of stroke differ between infants and older children?

Infants and neonates commonly present with **seizures**, whereas older children have **acute hemiplegia**.

Calder K, Kokorowski P, Tran T, Henderson S. Emergency department presentation of stroke. *Pediatr Emerg Care.* 2003;19(5):320–328.

Children's Hemiplegia and Stroke Association. www.chasa.org. Accessed January 22, 2020.

51. What is the differential diagnosis of stroke in children?

Cerebrovascular disease, or *stroke,* can be the result of primary vascular disease, bleeding disorder (hemorrhagic stroke), or a variety of secondary problems that lead to thrombotic or embolic occlusions (most commonly of the middle cerebral artery). Diagnostic possibilities include the following:

- **Cardioembolic:** Cyanotic congenital heart disease, atrial myxoma, endocarditis, rheumatic or other valvular heart disease. This is accentuated with iron deficiency.

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- **Hematologic:** Hemoglobinopathies (especially sickle cell disease), hypercoagulable states (antithrombin III deficiency, protein C or S deficiency), hyperviscosity (leukemia, hyperproteinemia, thrombocytosis), coagulation disorders (lupus-associated antibodies, hemophilia, thrombocytopenia, factor V abnormalities, hyperhomocysteinemia)
- **Circulatory:** Vasculitis (infectious or inflammatory), occlusive (homocystinuria, arteriosclerosis, fibromuscular dysplasia of the internal carotid artery, posttraumatic carotid scarring), carotid or vertebral artery dissection, moyamoya disease, atrioventricular malformation with steal syndrome, anomalous circulation, posttraumatic air embolism, arterial aneurysm, hemiplegic migraine
- **Metabolic:** Mitochondrial disease

Morgan L. Evaluation and management of the child with suspected acute stroke. *Clin Pediatr Emerg Med.* 2017;16(1):29–36.
Gumer LB, Del Vecchio M, Aronoff S. Strokes in children: a systematic review. *Pediatr Emerg Care.* 2014;30(9):660–664.

52. What is moyamoya disease?

Moyamoya, which is Japanese for "puff of smoke," refers to the cerebral angiographic appearance of patients with this primary, vascular disease that causes stenosis of the arteries of the circle of Willis and carotid arteries and thus leads to prominent arterial collateral circulation. It occurs in a wide variety of conditions, such as neurofibromatosis type 1, sickle cell disease, Down syndrome, and tuberous sclerosis, in addition to the idiopathic, likely genetic vasculopathy that is endemic in Japan. Because it is a chronic condition, fine vascular collaterals can develop, and it is these collaterals that create the "puff of smoke" appearance on angiography (Fig. 13.2). Patients with moyamoya present with transient ischemic attacks, ischemic strokes, and seizures, although in children, the predominant manifestation is ischemia. Moyamoya disease may now be treated neurosurgically.

Lee S, Rivkin MJ, Kirton A, et al. Moyamoya disease in children: results from the International Pediatric Stroke Study. *J Child Neurol.* 2017;32(11):924–929.
Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. *N Engl J Med.* 2009;360(12):1226–1237.

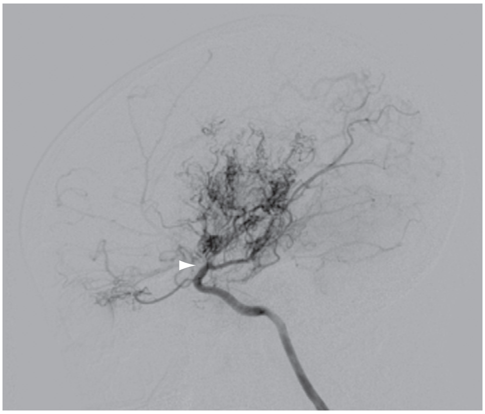

Fig. 13.2 Injection of the internal carotid artery (ICA) demonstrates findings consistent with moyamoya disease: stenosis of the distal ICA *(arrowhead)*, diminished filling of the middle and anterior cerebral artery branches, and the proliferation of collateral vessels, the "puff of smoke" finding. (From Winn HR, ed. *Youmans Neurological Surgery*. 6th ed. Philadelphia, PA: Saunders Elsevier; 2011:2145.)

53. A child who develops weakness, incontinence, and ataxia 10 days after a bout of influenza likely has what diagnosis?

Acute disseminated encephalomyelitis (ADEM) is thought to be a postinfectious or parainfectious process that is targeted against central myelin. Any portion of the white matter may be affected. Multiple lesions with a perivenular lymphocytic and mononuclear cell infiltration and demyelination are seen on pathologic examination. ADEM has been associated with mumps, measles, rubella, varicella-zoster, influenza, parainfluenza, mononucleosis, and some immunizations. An associated transverse myelitis may be acute (developing over hours) or subacute (developing over 1 to 2 weeks), with both motor and sensory tract involvement. Bladder and bowel dysfunction are often early and severe. CSF examination shows a mild increase of pressure and up to 250 cells/mm^3, with a predominance of lymphocytes. The MRI shows an increased T2 signal intensity. Prognosis, particularly with the use of intravenous corticosteroids, is generally good.

Gray MP, Gorelick MH. Acute disseminated encephalomyelitis. *Pediatr Emerg Care.* 2016;32(6):395–400.

54. In patients with acute injury to the brain, what two types of edema may occur?

- **Vasogenic edema** results from increased permeability of the capillary endothelium with resulting exudation. It is more marked in cerebral white matter and occurs as a result of inflammation (meningitis and abscess), focal processes (hemorrhage, infarct, or tumor), vessel pathology, or lead or hypertensive encephalopathy. On cranial CT scan, vasogenic edema shows up best with the administration of contrast.
- **Cytotoxic edema** results from the rapid swelling of cells, especially astrocytes, and also from neurons and endothelial cells as a result of dysfunction of the membranes and ionic pumps from energy failure, which may lead to cellular death. Hypoxia caused by cardiac arrest, hypoxic-ischemic encephalopathy (HIE), various toxins, severe infections, status epilepticus, infarct, or increased ICP is also a possible cause.

55. What are the treatments for increased ICP?

- **Hyperventilation:** The usual goal is to lower the P_{CO_2} to 25 to 30 mm in the acute situation. This causes vasoconstriction, which decreases the intracranial vascular volume.
- **Fluid restriction, osmotic diuretics**, and **hypertonic mannitol solution** all work to shrink brain water content, provided there is an intact blood–brain barrier (none of these are evidence-based for newborn infants).
- **Head elevation** in a midline position to 30 degrees maximizes venous return. Head elevation may worsen ICP in the presence of hypovolemia. The head should be kept midline to avoid venous compression.
- **External ventricular drain** (EVD) is sometimes placed, both to monitor pressure and to allow for a minimal amount of CSF withdrawal. An EVD may typically be used with intraventricular hemorrhage.
- **Normalization of physiologic parameters:** It is important to avoid significant hypotension, hypoxia, hypoglycemia, and hyperthermia.

56. How is brain death defined?

Brain death is defined by an irreversible absence of cortical and midbrain activity. Determination of brain death in term newborns, infants, and children is a clinical diagnosis based on the absence of neurologic function with a known irreversible cause of coma. Spinal cord, peripheral nerve, or reflex muscular activity may persist despite brain death. Decorticate or decerebrate posturing, however, is inconsistent with brain death. The examination must remain unchanged over time. Other countries have defined brain death as the absence of brainstem function alone, but in the United States, the absence of cortical function also must be demonstrated. The clinical hallmark of brain death is deep, unremitting, unresponsive coma.

De Georgia MA. History of brain death as death: 1968 to the present. *J Crit Care.* 2014;29(4):673–678.

Nakagawa TA, Ashwal S, Mathur M, et al. Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. *Crit Care Med.* 2011;39(9):2139–2155.

57. How is the diagnosis of brain death in children made?

Patients with suspected brain death should be observed and tested on two separate occasions (including neurologic examination and apnea testing) over 12 to 24 hours for the following:

- **Unresponsive coma** and the absence of eye opening, extraocular movements, vocalizations, or other cerebral-generated activity
- The complete **absence of brainstem function**, including nonresponsive, midposition, or fully dilated pupils; no spontaneous or reflexive eye movements on oculovestibular testing ("doll's eyes" and oculocaloric responses); no bulbar muscle function (i.e., corneal, gag, cough, sucking, and rooting reflexes); and no respirations on apnea testing
- **Apnea testing** with a rise of arterial P_{CO_2} at least 20 mm Hg above baseline and $\geq$60 mm Hg overall with no respiratory effort
- Ancillary testing (EEG and radionuclide cerebral blood flow) is not required and should not be used as a substitute, but may be used to supplement the neurologic examination and apnea testing.

Nakagawa TA, Ashwal S, Mathur M, et al. Clinical report—guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. *Pediatrics.* 2011;128(3):e720–e740.

58. How does one distinguish a persistent vegetative state from a minimally conscious state?

- The **persistent vegetative state** is "a form of eyes-open permanent unconsciousness in which the patient has periods of wakefulness and physiologic sleep/wake cycles, but at no time is the patient aware of himself or herself or the environment." If this state persists for more than 3 months in children, the long-term outlook is grim.
- The **minimally conscious state** occurs on emergence from the persistent vegetative state, and a patient must demonstrate a reproducible action in one or more of four types of behavior: (1) simple command following, (2) gestural or verbal "yes/no" responses, (3) intelligible verbalization, or (4) purposeful behaviors.

Hirschberg R, Giacino JT. The vegetative and minimally conscious states: diagnosis, prognosis and treatment. *Neurol Clin.* 2011;29(4):773–786.

59. What is the differential diagnosis of an intracranial bruit?

An *intracranial bruit* can be found in normal children and may be augmented by contralateral carotid compression. Disorders that may be associated with an intracranial bruit include vascular malformations and conditions characterized by increased cerebral blood flow:

- Fever
- Cerebral angioma
- Intracerebral tumors
- Thyrotoxicosis
- Cerebral aneurysm
- Any cause of increased ICP
- Anemia
- Cerebral arteriovenous malformations
- Meningitis
- Cardiac murmurs

Mace JW, Peters ER, Mathies AW Jr. Cranial bruits in purulent meningitis in childhood. *N Engl J Med.* 1968;278(26):1420–1422.

60. In a previously normal child who develops acute ataxia, what are the two most common diagnoses?

- **Drug ingestion**, especially of AEDs, heavy metals, alcohol, and antihistamines.
- **Acute postinfectious cerebellitis**, most commonly after varicella, is a diagnosis of exclusion if drug screening, CT or MRI, CSF evaluation, and other tests are negative.

Prasad M, Ong MT, Setty G, et al. 15 minute consultation: the child with acute ataxia. *Arch Dis Child Educ Pract Ed.* 2013;98(6): 217–223.

61. What are the causes of toe walking?

- CP (spastic diplegia)
- Hereditary spastic paraplegia (HSP)
- Muscular dystrophy
- Spinal dysraphism
- Hereditary or acquired polyneuropathies
- Intraspinal and filum terminale tumor
- Equinovarus deformity
- Isolated congenital shortening of the Achilles tendon
- Variation of normal in early stages of walking
- Normal development pattern in some toddlers

Oetgen ME, Peden S. Idiopathic toe walking. *J Am Acad Orthop Surg.* 2012;20(5):292–300.

62. What is the significance of a positive Babinski response?

Stimulation of the lateral aspect of the sole of the foot to the distal metatarsals may elicit an extensor plantar response (i.e., dorsiflexion of the big toe), known as a *positive Babinski* response or sign. Its presence can be normal up to 12 months of age. When it persists after this age, it can be a sign of disturbed pyramidal tract function. The stimulus elicits a number of sensory pathways with competing functions (including grip and withdrawal) and is somewhat dependent on the state of the infant and the examiner's technique. Its value as a localizing sign in the neonate is more controversial, but a consistent asymmetry is abnormal.

63. A 7-year-old child with progressive ataxia, kyphoscoliosis, nystagmus, pes cavus (high arch), and an abnormal electrocardiogram (ECG) likely has what diagnosis?

Friedreich ataxia. This heredodegenerative disease is an autosomal recessive disorder with childhood onset of gait ataxia, absent tendon reflexes, and extensor plantar responses. The spinal cord shows degeneration and sclerosis of the spinocerebellar tracts, the posterior column, and the corticospinal tracts. The condition is rare. The gene for Friedreich ataxia has been mapped to chromosome 9q13, contains a trinucleotide repeating sequence (GAA), and encodes for a protein called *frataxin*. A deficiency of frataxin leads to the accumulation of iron in the mitochondria and to oxidative stress, which leads to cell death.

Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. *Br Med Bull.* 2017;124(1):19–30.
Anheim M, Tranchant C, Koenig M. The autosomal recessive cerebellar ataxias. *N Engl J Med.* 2012;366(7):636–646.

64. What clinical features help distinguish peripheral from central vertigo?

Peripheral vertigo implies dysfunction of the labyrinth or vestibular nerve, whereas *central vertigo* is associated with abnormalities of the brainstem or temporal lobe.

Peripheral

- Hearing loss, tinnitus, and otalgia may be associated.
- Past pointing and falling in the direction of unilateral disease occur.
- In bilateral disease, ataxia occurs with the eyes closed.
- Vestibular and positional nystagmuses are present.

Central

- Cerebellar and cranial nerve dysfunction are frequently associated.
- No hearing loss is present.
- An alteration of consciousness may be associated.
- Vertigo is a common symptom with migraine.

Fenichel GM. *Clinical Pediatric Neurology: A Signs and Symptoms Approach.* 6th ed. Philadelphia, PA: Elsevier; 2009:365.

65. In what settings is hyperacusis noted?

Hyperacusis, or increased sensitivity to sound, is found in patients with injury to the facial nerve (cranial nerve [CN] VII), which innervates the stapedius muscle, or in those with injury to the trigeminal nerve (CN V), which innervates the tensor tympani muscle. Exaggerated startle response to sound or vibration occurs in patients with lysosomal storage diseases (e.g., sphingolipidoses such as Tay-Sachs disease, GM_1 gangliosidosis, and Sandhoff disease), Williams syndrome, hyperkalemia, tetanus, and strychnine poisoning.

66. What is the most common cause of neonatal asymmetric crying facies?

In this entity, with an incidence of approximately 1 per 160 live births, one side of the lower lip depresses during crying (on the normal side) and the other does not (Fig. 13.3). Often misdiagnosed as a facial nerve palsy resulting from forceps delivery, the most common cause is **congenital absence or hypoplasia of the depressor anguli oris muscle** of the lower lip. Although it is usually an isolated finding in most cases, the condition can be associated with 22q11.2 deletion syndrome and other congenital malformations, especially of the cardiovascular system.

Arya S, Jain SK, Richardson CJ. Facial asymmetry in a crying newborn: a comparison of two cases and review of literature. *Case Rep Pediatr.* 2017;2017:6368239.

Pasick C, McDonald-McGinn DM, Simbolon C, et al. Asymmetric crying facies in the 22q11.2 deletion syndrome: implications for future screening. *Clin Pediatr.* 2013;52:1144–1148.

Sapin SO, Miller AA, Bass HN. Neonatal asymmetric crying facies: a new look at an old problem. *Clin Pediatr.* 2005;44:109–119.

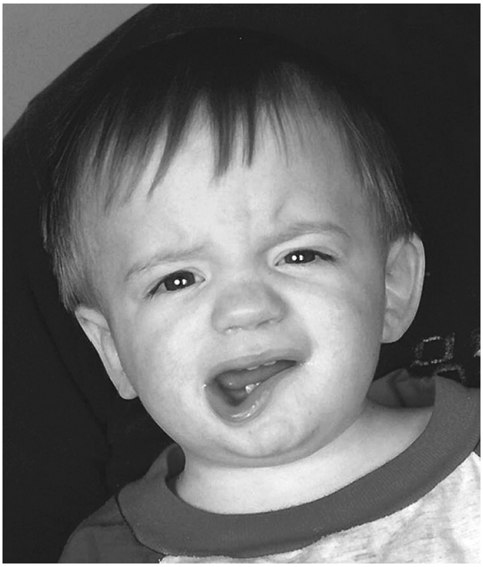

Fig. 13.3 Asymmetric crying facies. (From Terzis JK, Anesti K. Developmental facial paralysis: a review. *J Plast Reconst Aesthet Surg.* 2011;64:1318–1333, 1324.)

67. What are common causes of seventh-nerve (facial nerve) palsy?

Facial weakness caused by a lesion of the facial nerve (CN VII) is common. A seventh-nerve palsy is either central or peripheral in location. Any part of the nerve can be disturbed: the nucleus itself, the axon as it passes through the pons, or the peripheral portion of the nerve. In peripheral seventh nerve palsy, the facial weakness involves both the upper and lower face and affects both emotional and volitional facial movements. It should be noted that there may be other CN involvement, especially CN V, with hypesthesia or dysesthesia.

Etiologies include the following:

- **Trauma**
- **Developmental hypoplasia or aplasia**, including the Möbius anomaly
- **Bell palsy** (usually idiopathic, but may follow nonspecific viral infections)
- **Infections**, including Ramsay Hunt syndrome (herpes zoster invasion of the geniculate ganglion, producing herpetic vesicles behind the ear and painful paralysis of the facial nerve); Lyme disease; local invasion from suppurative mastoiditis or otitis media; mumps, varicella, Epstein-Barr virus, cytomegalovirus, rubella, HIV, or enterovirus neuritis; sequelae of bacterial meningitis; and parotid gland infection, inflammation, or tumor
- **GBS**
- **Tumor** of the brainstem or cerebellar pontine angle tumors
- **Inflammatory disorders** such as sarcoidosis

Spencer CR, Irving RM. Causes and management of facial nerve palsy. *Br J Hosp Med (Lond).* 2016;77(12):686–691.
Adour KK. Diagnosis and management of facial paralysis. *N Engl J Med.* 1982;307(6):348–351.

68. How is *peripheral* seventh-nerve palsy distinguished from *central* seventh-nerve palsy?

The patient with a suspected palsy is asked to wrinkle the forehead, raise the eyebrows, and close the eyes tightly. In *peripheral* seventh-nerve palsy, no forehead furrows are noted, and the affected eye does not open as wide as the unaffected eye. In *central* seventh-nerve palsy, forehead furrowing and relatively good eye opening occur because the cells of the facial nucleus that innervate the upper face receive bilateral innervation from fibers from both cerebral hemispheres. Lower facial muscles are innervated from only the single contralateral cerebral hemisphere.

Gilden DH. Bell's palsy. *N Engl J Med.* 2004;351(13):1323–1331.

69. During recovery from Bell palsy, why do the eyes water at mealtime?

These are **crocodile tears**. The facial nerve supplies autonomic motor function to the lacrimal and salivary glands. Because of aberrant reinnervation during the course of healing from a facial nerve palsy, tasting a meal can trigger tearing rather than salivation. Folklore has it that crocodiles feel compassion for their victims and weep while munching. This is called *synkinesis,* which may also involve the other muscles of the facial nerve or may be congenital.

70. When are "doll's eyes" movements considered normal or abnormal?

The *oculovestibular reflex* (also called *oculocephalic, proprioceptive head-turning reflex,* or *doll's eyes reflex*) is used most commonly as a test of brainstem function. The patient's eyelids are held open while the head is briskly rotated from side to side. A positive response is contraversive conjugate eye deviation (i.e., as the head rotates to the right, both eyes deviate to the left). Doll's eyes movements are interpreted as follows:

- *In healthy, awake newborn infants* (who cannot inhibit or override the reflex with willful eye movements), the reflex is easy to elicit and is a normal finding. It can be used to test the range of the extraocular movements of infants during the first weeks of life.
- *In healthy, awake, mature individuals,* normal vision overrides the reflex, which is thus normally absent, and so the eyes follow the head turning.
- *In a patient in a coma with preserved brainstem function,* the depressed cortex does not override the reflex, and doll's eyes movements occur in rapid head rotation. Indeed, the purpose of eliciting this reflex in the comatose patient is to demonstrate that the brainstem still functions normally.
- *In a patient in a coma with brainstem damage,* the neural circuits that carry out the reflex are impaired, and the reflex is abolished.

71. How are "cold calorics" done?

As a test of brainstem function in an obtunded or comatose individual, 5 mL of ice-cold water is placed in the external ear canal (after ensuring the integrity of the tympanic membrane), with the head elevated at 30 degrees. A normal response occurs with deviation of the eyes to the side in which the water was placed. No response indicates severe dysfunction of the brainstem and the medial longitudinal fasciculus. If done in the waking state, ipsilateral deviation occurs with nystagmus in the opposite direction.

72. What causes pinpoint pupils?

Pupillary size represents a dynamic balance between the constricting influence of the third nerve (representing the parasympathetic autonomic nervous system) and the dilating influence of the ciliary nerve (which conducts fibers of the sympathetic nervous system). Pinpoint pupils indicate that the constricting influence of the third cranial nerve is not balanced by opposing sympathetic dilation. Possible etiologies include the following:

- **Structural lesion in the pons** through which the sympathetic pathways descend (most commonly, hemorrhage)
- **Opiates**, such as heroin or morphine
- **Other agents**, including propoxyphene, organophosphates, carbamate insecticides, barbiturates, clonidine, meprobamate, pilocarpine eyedrops, and mushroom or nutmeg poisoning

73. What is the differential diagnosis of ptosis?

Ptosis is the downward displacement of the upper eyelid as a result of dysfunction of the muscles that elevate the eyelid. A drooping eyelid may represent pseudoptosis caused by swelling of the eyelid as a result of local edema or active blepharospasm. True ptosis results from weakness of the eyelid muscles or interruption of its nerve supply. Etiologies include the following:

- **Muscular:** Congenital ptosis, which may occur alone or in the setting of Turner or Smith-Lemli-Opitz syndrome, myasthenia gravis (associated with marked daytime fluctuation), botulism, or some muscular dystrophies
- **Neurologic:** Horner syndrome, which results from the interruption of the sympathetic supply to Müller smooth eyelid muscle, and third-nerve palsy, which innervates the levator palpebral muscle; brainstem or orbital tumor (concerning if blurred vision is also present)

74. What is a Marcus Gunn pupil?

An **afferent pupillary defect (APD)**. The pupils are normally equal in size (except for patients with physiologic anisocoria) as a result of the consensual light reflex: light entering either eye produces the same-strength "signal" for the constriction of both the stimulated and nonstimulated pupil. Some diseases of the maculae or optic nerves affect one side more than the other, such as multiple sclerosis or optic neuritis. For example, a meningioma may develop on one optic nerve sheath. As a result of unilateral or asymmetric optic nerve dysfunction, a Marcus Gunn pupil may result.

75. How is the swinging flashlight test done to detect a Marcus Gunn pupil?

- The patient is examined in a dim room, and fixation is directed to a distant target. This permits maximal pupillary dilation because of a lack of direct light and accommodation reflexes.
- Light presented to the "good" eye produces the equal constriction of both pupils. A flashlight is swung briskly over the bridge of the nose to the eye with the "defective" optic nerve. The abnormal pupil remains momentarily constricted from the lingering effects of the consensual light response. However, the impaired eye, with its reduced pupillomotor signal, soon escapes the consensual reflex and actually dilates, despite being directly stimulated with light. The pupil that paradoxically dilates to direct light stimulation displays the afferent defect.

EPILEPSY

76. What is epilepsy?

Epilepsy describes a syndrome of recurrent, unprovoked seizures, typically two or more, not the result of fever or a systemic medical condition. It is derived from the Greek verb *epilepsia,* meaning "to seize upon" or "to take hold of." The early Greeks referred to it as the sacred disease, but Hippocrates debunked this notion and argued from clinical evidence that it arose from the brain. Epilepsy is not an entity or even a syndrome, but rather a symptom complex arising from disordered brain function that itself may be the result of a variety of pathologic processes.

Chang BS, Lowenstein DH. Epilepsy. *N Engl J Med.* 2003;349(13):1257–1266.
American Epilepsy Society. www.aesnet.org. Accessed January 22, 2020.
Epilepsy Foundation. www.epilepsy.com. Accessed January 22, 2020.

77. What is the long-term outcome for children with epilepsy?

This is dependent on etiology. Children with idiopathic or genetically determined epilepsy have the best prognosis, whereas children with antecedent neurologic abnormalities fare less well. Nearly 75% of children will enter into a sustained remission 3 to 5 years after the onset of their epilepsy. There is no evidence that antiepileptic medications as they are currently used in clinical practice are neuroprotective or that they alter the long-term outcome of patients. Although there is a favorable prognosis for the remission of seizures, children with epilepsy are at an increased risk for having other long-term comorbidities, including difficulties achieving social, educational, and vocational goals. Treatment with antiepileptic medications is one important part of the management of the child, but other critical aspects of the physician–patient interaction, including educating, counseling, and advocacy, are equally important.

78. How often are EEGs abnormal in healthy children?

About 10% of "normal" children have mild, nonspecific abnormalities in background activity. About 2% to 3% of healthy children have unexpected incidental epileptiform (i.e., spikes or sharp wave) patterns. Some may have heritable, familial EEG abnormalities without a clinical seizure disorder (e.g., centrotemporal spikes seen in benign seizure-susceptibility syndromes such as rolandic epilepsy). In patients with migraines, the EEG may frequently have epileptiform features. There is a higher incidence of EEG abnormalities in autism, and the incidence of abnormalities may increase with subsequent EEGs.

79. Should an EEG be done on all children who have a first afebrile seizure?

This is a major controversial issue. Of new-onset seizures in children, about one-third do not involve fever. The American Academy of Neurology recommends that all children with a first seizure without fever undergo an EEG in order to best classify the epilepsy syndrome. Others argue that the quantity of expected information from obtaining EEGs for all cases is too low to affect treatment recommendations in most patients. They suggest that a selective approach to EEG use be pursued, particularly for (1) children with a seizure of focal onset, (2) children <1 year of age, and (3) any child with unexplained cognitive or motor dysfunction or abnormalities on neurologic examination.

Debicki DB. Electroencephalography after a single unprovoked seizure. *Seizure.* 2017;49:69–73.

Khan A, Baheerathan A. Electroencephalogram after first unprovoked seizure in children: routine, unnecessary or case specific. *J Pediatr Neurosci.* 2013;8(1):1–4.

Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children. Report of the Quality Standards Subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society. *Neurology.* 2000;55(5):616–623.

80. In a patient with a suspected seizure disorder but a normal EEG, how can the sensitivity of the EEG be increased?

- Repeat the standard EEG.
- Obtain after sleep deprivation.
- Use activation procedures: hyperventilation and photic stimulation (e.g., strobe lights).
- Increase the recording time: continuous EEG (>24 hours).

81. Which types of epilepsy are characterized by specific EEG findings?

- **Rolandic epilepsy:** bicentral spikes (only during sleep in 30%); “midtemporal spikes” is a misnomer, related to the positioning of the EEG electrodes in the temporal regions.
- **Benign epilepsy with occipital focus:** continuous unilateral or bilateral occipital high-voltage spike waves
- **Panayiotopoulos syndrome:** also known as early-onset occipital epilepsy; abnormal spikes in one or both occipital lobes.
- **Absence epilepsy:** characteristic 3-Hz spike-wave pattern
- **Juvenile absence epilepsy:** characteristic fast spike-wave pattern (>3 Hz)
- **Juvenile myoclonic epilepsy:** fast spikes and polyspike-wave patterns
- **Infantile spasms:** hypsarrhythmia, a markedly disorganized pattern
- **Lennox-Gastaut syndrome:** slow spike-wave forms at <3-Hz frequency
- **Landau-Kleffner syndrome:** continuous spike waves (electrical status epilepticus of sleep [ESES])

82. Should all children with a new-onset afebrile, unprovoked generalized seizure have a CT or MRI evaluation?

Although most adults with new-onset seizures should have a head imaging study (preferably MRI), the relatively high frequency of idiopathic seizure disorders in children often obviates a scan in those with generalized seizures, nonfocal EEGs, and normal neurologic examinations. Consider obtaining a cranial imaging study in the following situations:

- Any seizure with focal components (other than mere eye deviation)
- Newborns and young infants with seizures
- Status epilepticus at any age
- Focal slowing or focal paroxysmal activity on EEG

Crocker CE, Pohlmann-Eden B, Schmidt MH. Role of neuroimaging in first seizure diagnosis. *Seizure.* 2017;49:74–78.

83. Which disorders have clinical features that can mimic a seizure?

Many conditions are characterized by the sudden onset of transient abnormal consciousness, awareness, reactivity, behavior, posture, tone, sensation, or autonomic function. Syncope, breath-holding spells, migraine, hypoglycemia, narcolepsy, cataplexy, sleep apnea, gastroesophageal reflux, and parasomnias (night terrors, sleep walking, sleep talking, nocturnal enuresis) feature an abrupt or “paroxysmal” alteration of brain function and suggest the possibility of epilepsy.

84. What are ways to distinguish psychogenic nonepileptic seizures (PNES) from epileptic seizures?

PNES consist of changes in behavior (including motor manifestations) or consciousness that are not accompanied by electrophysiologic changes. PNES were formerly called *pseudoseizures* or *hysterical seizures,* but these terms are now discouraged. Features that help identify PNES include:

- *History*: Patient is more likely to have a history of psychiatric problems, including depression, anxiety, posttraumatic stress disorder, and somatoform disorder. Common precipitating factors: school-related difficulties and interpersonal conflict.

- *Clinical*: PNES are usually longer than 2 minutes, eyes are forcefully closed (compared with eyes typically open in epileptic seizures), motor activity is waxing and waning, vocalizations are commonly present (uncommon in epileptic seizures), incontinence is less common, awakening and reorientation are more rapid than epileptic seizures, and recall of event is more common in PNES than with an epileptic seizure.
- *Studies*: Video-EEG (most reliable to rule out epileptic seizures); ambulatory EEG; prolactin levels (typically elevated 15 to 20 minutes after an epileptic seizure but not after PNES).

Doss JL, Plioplys S. Pediatric psychogenic nonepileptic seizures: a concise review. *Child Adolesc Psychiatr Clin N Am.* 2018;27(1):53–61.

Korff CM, Nordlii DR Jr. Paroxysmal events in infants: persistent eye closure makes seizures unlikely. *Pediatrics.* 2005;116(4):e485–e486.

85. What are the categories of seizures in children?

The syndrome classification as codified in the International Classification of Epileptic Seizures by the International League Against Epilepsy (ILAE) distinguishes seizures on the basis of *type* rather than *etiology* (Table 13.2). In 2010, the classification was revised with elimination of terms previously used for focal seizures, such as "simple partial," "complex partial," and "partial seizures secondarily generalized" as being too imprecise. These were replaced with a classification that included *generalized seizures,* which occur in and rapidly engage bilaterally distributed networks, while *focal seizures* are more limited to one hemisphere, either discretely localized or more widely distributed in that hemisphere. Although the classification for generalized seizures was straightforward, the ILAE believed that there was inadequate information to create a scientific classification for focal seizures but that focal seizures should be described according to their manifestations (e.g., dyscognitive with impairment of consciousness/awareness, focal motor). In 2017, the classification underwent another minor revision with the addition of another category: "generalized and focal epilepsy" to encompass epilepsy syndromes with both features (e.g., Dravet syndrome, Lennox-Gastaut syndrome). Additionally, previous terminology by the ILAE categorized the causes of seizures into *symptomatic* (due to a known disorder of the CNS), *cryptogenic* (due to a hidden or occult cause), or *idiopathic* (no known cause except a possible hereditary predisposition). This terminology was believed to be confusing and was eliminated. New etiologic categories involve three groups: *genetic, structural/metabolic,* and *unknown.*

Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for classification and terminology. *Epilepsia.* 2017;58(4):522–530.

Table 13.2 International League Against Epilepsy Classification of Seizures

Generalized
Tonic-clonic (in any combination)
Absence
Typical
Atypical
Absence with special features
Myoclonic absence
Eyelid myoclonic
Myoclonic
Myoclonic
Myoclonic atonic
Myoclonic tonic
Clonic
Tonic
Atonic
Focal seizures
Generalized and focal seizures
Unknown
Epileptic spasms (infantile spasms)

Adopted from Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission on classification and terminology. *Epilepsia.* 2017;58(4):522–530.

86. What are structural and metabolic causes of seizures?

See Table 13.3.

Table 13.3 Structural and Metabolic Causes of Seizures

Fever • Simple febrile seizures • Complicated febrile seizures
Trauma • Impact seizures • Early posttraumatic seizures • Late posttraumatic seizures
Hypoxia • Complicated breath-holding spells • Hypoxic seizures
Metabolic • Acquired metabolic disorders • Neurologic effects of systemic disease • Inborn errors of metabolism
Toxins • Drugs • Drug withdrawal • Biologic toxins
Stroke • Ischemic stroke • Embolic stroke • Hemorrhagic stroke
Intracranial Hemorrhage • Subdural hemorrhage • Subarachnoid hemorrhage • Intracerebral hemorrhage
CNS Malformation • Cerebral atrophy • Cortical dysplasia • Microcephaly

CNS, Central nervous system.
Adapted from Evans OB. Symptomatic seizures. *Pediatr Ann.* 1999:28(4):231–237.

87. If a previously normal child has an afebrile, generalized tonic-clonic seizure, what should parents be told about the risk for recurrence?

Studies indicate that the recurrence rate is between 25% and 50%. The EEG is an important predictor of recurrence. A subsequent normal EEG reduces the 5-year recurrence risk to 25%. Occurrence of the seizure during sleep increases the risk to 50%. Half of recurrences will occur during the first 6 months after the first seizure; two-thirds will occur within 1 year, and 90% or more will have occurred within 2 years. The child's age at the time of the first seizure and the duration of the seizure do not affect the recurrence risk.

Mizorogi S, Kanemura H, Sano F, et al. Risk factors for seizure recurrence in children after first unprovoked seizure. *Pediatr Int.* 2015;57(4):665–669.
Shinnar S, Berg AT, Moshe SL, et al. The risk of seizure recurrence after a first unprovoked afebrile seizure in childhood: an extended follow-up. *Pediatrics.* 1996;98(2 Pt 1):216–225.

88. What are the most common inherited seizure or epilepsy syndromes?

- Febrile convulsions
- Rolandic epilepsy, childhood absence epilepsy
- Juvenile myoclonic epilepsy (of Janz)

89. What are the clinical features of rolandic epilepsy?

Rolandic epilepsy is an idiopathic localization-related epilepsy that represents 10% to 15% of all childhood seizure disorders.

- It begins in school-age children (4 to 13 years old) who are otherwise healthy and neurologically normal.
- Seizures are idiopathic or familial (autosomal dominant inheritance with age-dependent penetrance).

- Seizures may be simple or complex and partial or generalized. Classically, there is a history of one-sided facial paresthesias and twitching and drooling that may be followed by hemiclonic movements or hemitonic posturing. Consciousness is typically preserved. The seizures are primarily nocturnal and may secondarily generalize.
- Often referred to as *benign* because the individual is developmentally normal, seizures are usually rare and nocturnal, and they most often resolve after puberty.
- Many children may have one or only several seizures, so AED treatment is not mandatory, especially when seizures are nocturnal.
- Treatment is indicated when seizures occur in the daytime (diurnal) or if escalating in frequency.

90. What distinguishes typical and atypical absence seizures?

Typical absence

- *EEG*: 3-Hz spike wave; may be activated by hyperventilation or intermittent photic stimulation
- *Observations*: Abrupt onset and ending (typically 5 to 10 seconds)
- *Simple subtype*: Unresponsiveness with no other associated features except minor movements (e.g., lip smacking or eyelid twitching)
- *Complex subtype*: Unresponsiveness with more prolonged (>5 to 10 seconds) mild atonic, myoclonic, or tonic features or automatisms

Atypical absence (most common in Lennox-Gastaut syndrome)

- *EEG*: 2-Hz (or slower) spike wave
- *Observations*: Gradual onset and ending; frequency is more cyclic; unresponsive with more prolonged and pronounced atonic, tonic, myoclonic, or tonic activity

91. In a child who is suspected of having absence seizures, how can a seizure be elicited during an examination?

Hyperventilation for at least 3 minutes is a useful provocative maneuver to precipitate an absence seizure. Young patients may be coaxed into overbreathing by making a game of it. Hold a tissue paper or pinwheel in front of the child's mouth, and then instruct the patient to keep breathing fast enough to keep the tissue aloft or the pinwheel spinning.

92. What percentage of patients with absence seizures also have occasional grand mal seizures?

About **30 to 50%**; these may occur years later.

93. What is the prognosis for children with absence epilepsy?

The prognosis for patients with childhood absence epilepsy has been studied prospectively; nearly 90% of patients who have normal intelligence, normal neurologic examination, normal EEG background activity, no family history of convulsive epilepsy, and no history of tonic-clonic convulsions will have seizures that remit. Conversely, the complete absence of favorable factors is associated with a poor prognosis for the cessation of seizures. Absence seizures can be associated with various epilepsy syndromes, which have different underlying pathophysiologies and thus different prognoses. A typical absence seizure associated with childhood absence epilepsy may be genetic in origin, whereas an atypical absence seizure, which could be associated with Lennox-Gastaut epilepsy, may be symptomatic of brain injury. Although many children with absence seizures have favorable likelihoods of seizure resolution by adolescence, other comorbidities, including behavioral and psychiatric problems (e.g., attention-deficit/ hyperactivity disorder [ADHD], anxiety, depression) are common, even in the absence of seizures.

Vega C, Guo J, Killory B, et al. Symptoms of anxiety and depression in childhood absence epilepsy. *Epilepsia.* 2011;52(8):e70–e74.

94. A teenager, like his father, develops brief, bilateral, intermittent jerking of his arms, often in the morning upon awakening. What seizure disorder is he likely to have?

Juvenile myoclonic epilepsy, which is also called *myoclonic epilepsy of Janz,* is a familial form of primary idiopathic generalized epilepsy that typically involves "fast" 3- to 5-Hz spike-wave discharges on EEG ("impulsive petit mal") and autosomal dominant inheritance. The distinctive clinical features of this type of epilepsy include morning myoclonic jerks, generalized tonic-clonic seizures upon awakening, normal intelligence, a family history of similar seizures, and onset between the ages of 8 and 20 years.

95. What are myoclonic seizures?

These seizures are characterized by rapid, bilateral, symmetric muscle contractions of short duration—"quick jerks." They may be isolated, or they may occur repetitively. *Myoclonic seizures* may be the sole manifestation of epilepsy, or more commonly, they may be associated with absence seizures or tonic-clonic seizures. By definition, a myoclonic seizure lasts less than 100 μsec.

KEY POINTS: EPILEPSY

1. Definition: Repeated, unprovoked seizures
2. Classified as localization-related: focal or generalized
3. Main etiologic categories: genetic, structural/metabolic, and unknown
4. Compared with older children with new-onset seizures, infants are more likely to have results from EEG and neuroimaging that affect diagnosis and prognosis.
5. Proper classification of epilepsy syndromes provides guidance for treatment options and prognoses.

96. What distinguishes atonic and akinetic seizures?

An *atonic seizure* involves the sudden and usually complete loss of tone in the limb, neck, and trunk muscles. Muscle control is lost without warning, and the child may be seriously injured. This situation is often aggravated by the occurrence of one or more myoclonic jerks immediately before muscle tone is lost so that the fall is associated with an element of propulsion. Atonic seizures are particularly common in children with static encephalopathies, and they may prove refractory to therapy. In an *akinetic seizure,* movement is arrested without a significant loss of muscle tone; this is rare.

97. Which seizure types constitute the "epileptic encephalopathies"?

Epileptic encephalopathies constitute a group of diverse disorders that occur early in life with generalized or focal seizures resistant to pharmacology; they have persistent, severe EEG abnormalities and cognitive dysfunction with deterioration. The prototypical genetic epilepsy in this category is Dravet syndrome, also known as *severe myoclonic epilepsy of infancy (SMEI),* which is characterized by mutations in the sodium channel *SCN1A* gene. Other ion channel and non–ion-channel genetic defects are being identified. Other epileptic encephalopathies include Ohtahara syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and epileptic (infantile) spasms. Epileptic encephalopathies may be associated with de novo genetic mutations.

Kalser J, Cross JH. The epileptic encephalopathy jungle—from Dr West to the concepts of aetiology-related and developmental encephalopathies. *Curr Opin Neurol.* 2018;31(2):216–222.

Nieh SE, Sherr EH. Epileptic encephalopathies: new genes and new pathways. *Neurotherapeutics.* 2014;11(4):796–806.

98. What should be the sequence of genetic testing in pediatric epilepsy?

Deciding upon the genetic testing needed for pediatric epilepsy starts with identifying the seizure type and the epilepsy syndrome. If there are associated dysmorphic features or intellectual disability, then a karyotype or chromosomal microarray may be appropriate. If a specific epilepsy syndrome is identified, such as neonatal familial seizures, or Dravet syndrome, starting with a targeted gene panel would be appropriate. If these tests are not revealing, then whole-exome sequencing may provide some answers. In general, whole-exome sequencing identifies a cause in 25% of previously unknown disorders.

Helbig I, Heinzen EL, Mefford HC. Genetic literacy series: primer Part 2-Paradigm shifts in epilepsy genetics. *Epilepsia.* 2018;59(6):1138–1147.

Helbig I, Heinzen EL, Mefford HC. Primer Part 1: the building blocks of epilepsy genetics. *Epilepsia.* 2016;57(6):861–868.

Yang Y, Muzny DM, Reid JG, et al. Clinical whole exome sequencing for the diagnosis of Mendelian disorders. *N Engl J Med.* 2013;369(16):1502–1511.

99. Which of the pediatric epilepsies are associated with somatic genetic mutations?

A *somatic genetic mutation* is one that is acquired by a cell (and passed along in the course of cell division). This contrasts to a germline mutation that occurs in a gamete and may be passed to offspring as an inherited genetic alteration. Somatic mutations can be seen in hemimegaloencephaly (*AKT3* gene), a cause of epileptic spasms, that may be amenable to epilepsy surgery or in Sturge-Weber syndrome (*GNAQ* gene).

Poduri A, Evrony GD, Cai X, Walsh CA. Somatic mutation, genomic variation, and neurological disease. *Science.* 2013;341(6141): doi:10.1126/science.1237758.

Shirley MD, Tang H, Gallione CJ, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. *N Engl J Med.* 2013;368(21):1971–1979.

100. What is the most common genetic abnormality associated with Dravet syndrome?

***SCN1A* mutation**. *Dravet syndrome,* originally called SMEI, is an epilepsy syndrome that is characterized by febrile and afebrile seizures, usually within the first year of life, followed by myoclonus, atypical absence, and focal seizures. Dravet syndrome is an example of a channelopathy—a disease cause by dysfunction of ion channel subunits. The *SCN1A* mutation, first identified in 2001, results in an abnormality of the voltage-gated sodium channel alpha-1 subunit. AEDs that work on the sodium channel, such as carbamazepine, oxcarbazepine, phenytoin, or lamotrigine, may worsen seizures.

Wirrell EJ, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. *Pediatr Neurol.* 2017;68:18–34.e3.
Millichap JJ, Koh S, Laux LC, Nordli DR Jr. Dravet syndrome: when to suspect the diagnosis. *Neurology.* 2009;73(1):e59–e62.

101. What is the classic triad of epileptic (infantile) spasms?

Spasms, hypsarrhythmia, and developmental regression. Epileptic (infantile) spasms are also known as *West syndrome.* The condition is named for the physician who first described the condition in his own son in 1841. The term “epileptic spasms,” rather than “infantile spasms,” is preferred, as some cases can present outside infancy.

102. What characterizes hypsarrhythmia?

The term means “mountainous slowing,” and it describes the classic interictal EEG of epileptic (infantile) spasms that is characterized by extremely high-voltage ($>200\ \mu V$), slow, and disorganized brain waves with multifocal spike activity. Hypsarrhythmia may either precede or follow the onset of epileptic spasms. This EEG configuration may appear first or most obviously in non–rapid eye movement sleep and confirms the clinical diagnosis of epileptic spasms.

It should be noted that the presence of hypsarrhythmia is not a prerequisite for epileptic spasms.

103. How commonly is a cause identified in epileptic spasms?

A cause can be identified in **up to 90%** of children with epileptic spasms, particularly in those who are symptomatic at the time of the initial seizure. Of identifiable causes, three-fourths are prenatal or perinatal and one-fourth are postnatal. All patients with epileptic spasms should have detailed neuroimaging, metabolic, and genetic studies. Specific gene mutations are now identified in many patients previously considered “cryptogenic.”

Causes, including some possible specific examples, include the following:

- *Prenatal and perinatal:* Neurocutaneous disorders (tuberous sclerosis), brain injury (HIE), intrauterine infection (cytomegalovirus), brain malformations (lissencephaly, agenesis of the corpus callosum), inborn metabolic errors (nonketotic hyperglycinemia, phenylketonuria, maple syrup urine disease, pyridoxine dependency)
- *Postnatal:* Infectious (herpes encephalitis), HIE, head trauma

104. What is the prognosis for infants with epileptic spasms?

Prognosis in large part depends on the underlying etiology and the clinical state at the time of the first seizure. In the group with an unknown cause (10% to 15%), development, neurologic examination, and imaging studies are usually normal at the onset. With adrenocorticotropic hormone (ACTH) treatment, up to 40% will have a complete or near-complete recovery with normal cognitive development. In the group with a known structural/metabolic cause (85% to 90%), neurologic deficits, developmental delays, or cranial abnormalities are typically present before the first seizure. In this group, complete or near-complete recovery is achieved by only 5% to 15%. Twenty-five percent to 50% will develop Lennox-Gastaut syndrome. Regression may be seen before the onset of epileptic spasms, especially in visual or motor function.

Widjaja E, Go C, McCoy B, Snead OC. Neurodevelopmental outcome of infantile spasms: a systematic review and meta-analysis. *Epilepsy Res.* 2015;109:155–162.
Kivity S, Lerman P, Ariel R, et al. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. *Epilepsia.* 2004;45(3):255–262.

105. What is the treatment of choice for epileptic spasms?

Currently in the United States, most children with epileptic spasms are treated with **ACTH** as the first treatment option, with a positive response rate of approximately three-fourths of patients. Vigabatrin has been shown to be superior to ACTH for children with tuberous sclerosis, with a 95% spasm cessation rate. Vigabatrin may cause visual field defects, including visual field constriction and retinal toxicity, which may increase with duration of treatment and mandates periodic assessment with electroretinograms. Vigabatrin may also cause abnormal enhancement or restricted diffusion on MRI of the deep gray matter (thalamus, basal ganglia, and brainstem), which is reversible after cessation of treatment. High-dose prednisolone is now also used. If these treatment options fail, the ketogenic diet should be considered. If focality is present, epilepsy surgery may be a consideration.

Wilmshurst JM, Ibekwe RC, O’Callaghan FJK. Epileptic spasms—175 years on: trying to teach an old dog new tricks. *Seizure.* 2017;44:81–86.
Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2012;78(24):1974–1980.
Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. *Epilepsia.* 2010;51(10):2175–2189.

106. What is the most likely diagnosis in a child of Ashkenazi descent with stimulus-sensitive seizures, cognitive deterioration, and a cherry-red spot?

The classic lysosomal lipid storage disorder presenting symptoms of a progressive encephalopathy during infancy is **Tay-Sachs disease**. The infantile forms of GM_2 gangliosidosis include Tay-Sachs disease, which is caused by a deficiency of hexosaminidase A; and Sandhoff disease, which is caused by a deficiency of hexosaminidase A and B. Tay-Sachs is an autosomal recessive disorder that is localized to chromosome 15, with an incidence of 1 in 3900 in the Ashkenazi Jewish population of Eastern or Central European descent. The enzymatic defect leads to intraneuronal accumulation of GM_2 ganglioside. Normal development is seen until 4 to 6 months of age, when hypotonia and a loss of motor skills occur, with the subsequent development of spasticity, blindness, and macrocephaly. The classic cherry-red spot is present in the ocular fundi of more than 90% of patients (Fig. 13.4).

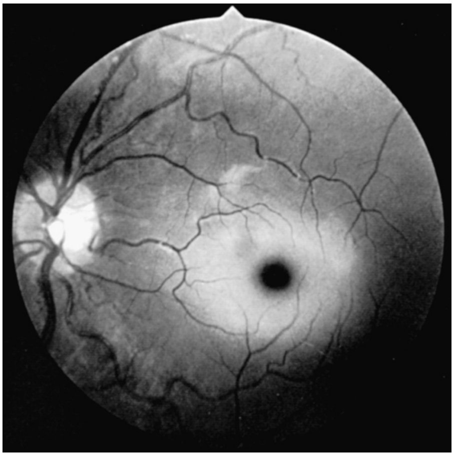

Fig. 13.4 A cherry red spot in a patient with GM_1 gangliosidosis. Note the whitish ring of sphingolipid-laden ganglion cells surrounding the fovea. (From Kleigman RM, Stanton BF, Schor NF, et al, eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:2072.)

107. A patient with seizures, microcephaly, and a low CSF glucose but a normal serum glucose has what likely condition?

The **GLUT-1 deficiency syndrome**, previously referred to as the *glucose transporter protein deficiency syndrome,* was first described in 1991. The clinical phenotype is variable, but the child usually presents with symptoms during the first years of life, with seizures and delays of motor and mental development. Movement disorders, including oculomotor abnormalities, dystonia, ataxia, myoclonus, and spasticity, are also seen. Growth of the head circumference slows during the first years of life. The diagnosis should be suspected if CSF reveals low glucose (and lactate) concentrations without evidence of inflammation and serum blood sugars are normal. The ketogenic diet is the gold standard of treatment, although a modified Atkins diet has also been shown to be effective. GLUT-1 deficiency syndrome is associated with a mutation in the *SLC21A* gene.

Akman CI, Yu J, Alter A, et al. Diagnosing glucose transporter 1 deficiency at initial presentation facilitates early treatment. *J Pediatr.* 2016;171:220–226.

Pong AW, Geary BR, Engelstad KM, et al. Glucose transporter type 1 deficiency syndrome: epilepsy phenotypes and outcomes. *Epilepsia.* 2012;53(9):1503–1510.

108. What is the clinical triad of Lennox-Gastaut syndrome?

Lennox-Gastaut syndrome is characterized by **intellectual disability**, **seizures** of various types, and disorganized **slow spike-wave activity** on an EEG (defined as frequency <3 Hz). The seizures usually begin during the first 3 years of life and are characteristically severe and refractory to anticonvulsant drugs. Prognosis is poor, with more than 80% of children continuing to have seizures into adulthood.

Resnick T, Sheth RD. Early diagnosis and treatment of Lennox-Gastaut syndrome. *J Child Neurol.* 2017;32(11):947–955.

109. A 5-year-old with a history of normal language development who develops seizures and inattention to speech with severe regression of language skills has what likely condition?

Landau-Kleffner syndrome. First described in 1957, this is a condition of acquired epileptic aphasia with nocturnal EEG abnormalities, reduction in language function, and problems with attention. Treatment should be with AEDs that are “spike suppressors.” Despite the use of various AEDs, benzodiazepines (diazepam or clobazam), or corticosteroids, recovery is often delayed, and communication problems persistent. These may be associated with mutations in the *GRIN2A* gene, which encodes a protein (GluN2A) that is a component of a subset of N-methyl-D-aspartate (NMDA) receptors. NMDA receptors are involved in synaptic plasticity and normal brain development.

Conroy J, McGettigan PA, McCreary D, et al. Towards the identification of a genetic basis for Landau-Kleffner syndrome. *Epilepsia.* 2014;55(6):858–865.

110. How is status epilepticus defined?

- Because of uncertainty regarding at precisely what time morbidity ensues in the course of a prolonged seizure, there is a *variance* in definitional length regarding status epilepticus. In general, >30 minutes of continuous or sequential seizure activity without return of consciousness has previously defined status epilepticus. The operational definition for status epilepticus, however, is 5 minutes, at which time a prolonged seizure is likely to become continuous, and thus treatment should be considered or started.
- Recurrent seizures without full recovery of consciousness between seizures.
- The ILAE now recommends 5 minutes as the time to treat for a generalized convulsion and 10 minutes for a nonconvulsive or focal seizure.

Trinka E, Cock H, Hesdorfer D, et al. A definition and classification of status epilepticus—report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia.* 2015;56(10):1515–1523.
Lowenstein DH, Bleck T, MacDonald RL. It's time to revise the definition of status epilepticus. *Epilepsia.* 1999;40(1):120–122.

111. Why is status epilepticus so dangerous?

With the onset of a seizure, catecholamine release and sympathetic discharge result in increased heart rate and blood pressure. Cerebral flow increases dramatically to compensate for the increased metabolic needs of the brain. With persistence of the seizure, compensatory mechanisms begin to fail. Respiratory acidosis and metabolic acidosis develop. Systemic blood pressure falls and ICP increases. The inability to meet the increased oxygen demands of the brain results in an intracranial switch to anaerobic metabolism, with acidosis, increased CSF lactate, and cerebral edema. The prolonged electrical discharges by themselves may also cause neuronal damage, referred to as *excitotoxicity*.

Lothman E. The biochemical basis and pathophysiology of status epilepticus. *Neurology.* 1990;40(Suppl 2):13–23.

112. What should be done in the first 5 minutes for a child who presents with an ongoing seizure?

- **0 to 5 minutes:** Confirm the diagnosis. Maintain noninvasive airway protection by head positioning or oropharyngeal airway. Administer 100% nasal oxygen. Suction as needed. Obtain and frequently monitor vital signs using pulse oximetry and ECG. Establish an intravenous (IV) or intraosseous (IO) line. Obtain venous blood for laboratory determinations (e.g., glucose, serum chemistries, hematology studies, liver function studies, toxicology screen, culture, anticonvulsant levels if patient is a known epileptic). Administer antipyretics as indicated. If hypoglycemic (or if a rapid reagent strip for glucose testing is not available), administer 2 mL/kg of $D_{25}W$ or 5 mL/kg of $D_{10}W$.
- **5 minutes:** If IV/IO access is present, administer lorazepam, 0.1 mg/kg (max: 4 mg) IV/IO at 2 mg/min. If IV/IO access cannot be established, options include (1) diazepam: rectal, 2 to 5 years, 0.5 mg/kg; 6 to 11 years, 0.3 mg/kg; ≥12 years, 0.2 mg/kg (max: 20 mg) and (2) midazolam: intramuscular or intranasal, 0.2 mg/kg (max: 10 mg); buccal, 0.5 mg/kg (max: 10 mg). Repeat lorazepam or one-half midazolam dose in 5 to 10 minutes if seizures persist.

Smith DM, McGinnis EL, Walleigh DJ, Abend NS. Management of status epilepticus in children. *J Clin Med.* 2016;5(4):E47.
Abend NS, Loddenkemper T. Pediatric status epilepticus management. *Curr Opin Pediatr.* 2014;26(6):668–674.

113. What is the most common cause of refractory seizures?

An **inadequate serum concentration of antiepileptic medication** is the most common cause of persistent seizures, but other causes should be considered:

- **Drug toxicity**, especially with phenytoin, may manifest by deteriorating seizure control.
- **Electrolyte disorders**, especially with an acute illness.
- **Metabolic abnormalities**, particularly in patients with inborn errors of metabolism, such as a mitochondrial disorder.
- **Medications** may have a paradoxical reaction and exacerbate certain types of seizures, particularly in children with mixed seizure disorders. For example, carbamazepine or phenytoin may control generalized tonic-clonic seizures in patients with juvenile myoclonic epilepsy, but may aggravate myoclonic and absence seizures.
- **Incorrect identification** of the epilepsy syndrome may be a cause. Partial seizures may masquerade as a generalized form of epilepsy in the very young child (bilateral symmetric tonic posturing may be seen in partial seizures). Conversely, generalized forms of epilepsy may first appear as partial seizures (severe infantile myoclonic epilepsy). Treatment based on an epilepsy syndrome rather than ictal semiology usually improves control in these circumstances.

114. What is the role of the ketogenic diet for the treatment of seizures?

The *ketogenic diet* is effective for the treatment of all seizure types, particularly in children with myoclonic forms of epilepsy. The diet involves supplying most calories through fats, with concurrent limitation of carbohydrates and protein. The mechanism of seizure control is unclear, but it is perhaps related to a switch in the cerebral metabolism from the use of glucose to the use of β-hydroxybutyrate. After 24 hours of fasting, the child is placed on a high-fat diet in which the ratio of fats to carbohydrates and protein combined is 3:1 to 4:1. Anticonvulsant drugs may be reduced or eliminated entirely if the diet is effective. The regimen must be followed closely, and parents must understand the demands of close adherence to the diet. A skilled dietitian is instrumental for providing variety and palatability to the diet. It is important to recall that the diet may have adverse effects, including serious, potentially life-threatening complications such as hypoproteinemia, lipemia, and hemolytic anemia. Variants of the ketogenic diet include the modified Atkins diet and the low glycemic index. β-Hydroxybutyrate levels are used to assess the degree of acidosis (similar to a drug level).

Jagadish S, Payne ET, Wong-Kisiel L, et al. The ketogenic diet and modified Atkins diet therapy for children with refractory epilepsy of genetic etiology. *Pediatr Neurol.* 2019;94(5):32–37.

Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. *J Child Neuro.* 2009;24(8):979–988.

115. What is the role of the vagus nerve stimulator (VNS) in seizure control?

The *VNS* is a surgically implanted device that intermittently stimulates the left vagus nerve. Why this decreases seizure frequency is not well understood, although it causes alterations in epinephrine release and is thought to increase GABA levels in the brainstem. It is a palliative—not curative—procedure that has been performed in adults and children with intractable complex partial seizures or generalized tonic seizures who are not considered candidates for definitive surgical cure. The VNS has been placed in children as young as 2 to 3 years old.

Elijamel S. Mechanism of action and overview of vagus nerve stimulation technology. In Elijamel S, Slavin KV, eds. *Neurostimulation: Principles and Practice*. Oxford: Wiley Blackwell; 2013:111–120.

116. What should a teenager with epilepsy be told about the potential of obtaining a driver's license?

State requirements vary regarding individuals with epilepsy and the right to drive. The most common requirement is a specified seizure-free period and submission of a physician's evaluation of the patient's ability to drive safely. Many states require the periodic submission of medical reports while the license is active. In addition, many states allow exceptions under which a license may be issued for a shorter seizure-free period (e.g., if a seizure occurred in isolation as a result of medication change or intercurrent illness), or they may issue licenses with restrictions (e.g., daytime driving only). A summary of requirements for each state is available from the Epilepsy Foundation.

Epilepsy Foundation. www.epilepsy.com/living-epilepsy/driving-and-transportation. Accessed January 22, 2020.

117. What are some common seizure triggers about which families should be counseled?

- Sleep deprivation, insufficient sleep, being overtired
- Fever and illnesses, particularly viral
- Low blood sugar, poor oral intake
- Flashing bright lights or patterns
- Association with menses
- Alcohol or drug use
- Stress
- Excess caffeine

Epilepsy Foundation. www.epilepsy.com/learn/triggers-seizures. Accessed January 22, 2020.

118. When should a child be referred for possible epilepsy surgery?

Although many epilepsy syndromes in childhood have spontaneous remission, 20% of incident epilepsy is intractable, and 5% of patients with intractable epilepsy may benefit from epilepsy surgery. Indications for surgery include failure of two AEDs, intractable disabling seizures, and/or deteriorating development. In general, outcome is determined by the completeness of the evaluation and the congruence of the data, the completeness of the resection, and the etiology of the seizures.

Ryvlin R, Cross JH, Rheims S. Epilepsy surgery in children and adults. *Lancet Neurol.* 2014;13(11):1114–1126.

FEBRILE SEIZURES

119. How are febrile seizures defined?

Febrile seizures are defined as a convulsion caused by a fever (temperature ≥100.4°F or 38°C by any method) without evidence of CNS pathology or acute electrolyte imbalance that occurs in children between the ages of 6 months and 60 months, with a peak at the end of the second year of life). Children with a history of epilepsy who have an exacerbation of seizures with fever are excluded. Febrile seizures occur in 2% to 5% of children. There is often a positive family history of febrile convulsions.

120. What is the likelihood of recurrence of a febrile seizure?

The likelihood of recurrence increases with a younger age of onset, with a recurrence rate about 1 in 2 if the patient is <1 year of age when the initial seizure occurs and 1 in 5 if the patient is >3 years of age at the time of the initial seizure. About half of recurrences are within 6 months of the first seizure; three-fourths occur within 1 year, and 90% occur within 2 years. Other risk factors for recurrence are a lower temperature (close to 100.4°F [38°C]) at the time of seizure, <1 hour duration of fever before the seizure, and a family history of febrile seizures. Overall, the recurrence rate in the pediatric population is about 30%.

AAP Subcommittee on Febrile Seizures. Clinical practice guideline—febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics.* 2011;127(2):389–394.

121. What features make a febrile seizure complex rather than simple?

- *Simple febrile seizure:* Relatively brief (<15 minutes long) and occurs as a solitary event (one attack in 24 hours) in the setting of fever not caused by CNS infection
- *Complex (also called atypical or complicated) febrile seizure:* Focal features either at the onset or during the seizure, extended in duration (>15 minutes long), or occurring more than once in 24 hours.

122. Why are complex febrile seizures more worrisome than simple febrile seizures?

They suggest a more serious problem. For example, a focal seizure raises concern of a localized or lateralized functional disturbance of the CNS. An unusually long seizure (>15 minutes) also raises the suspicion of primary CNS infectious, structural, or metabolic disease. Repeated seizures within a 24-hour period likewise imply a potentially more serious disorder or impending status epilepticus.

123. When should an LP be performed as part of the evaluation of a child <12 months of age with a simple febrile seizure?

This had traditionally been a difficult question when a well-appearing infant or young toddler was examined after a febrile seizure, but the widespread use of immunizations in the United States for two of the most common causes of bacterial meningitis, *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae,* has significantly lowered the incidence of bacterial meningitis. Current data no longer support a routine LP in a well-appearing, fully immunized child with a simple febrile seizure.

The American Academy of Pediatrics recommends an LP in any child who presents with a fever and seizure if the child has meningeal signs and symptoms (neck stiffness, Kernig, and/or Brudzinski signs) or any history or examination suggestive of intracranial infection. An LP should be *considered*:

- If the patient is between 6 and 12 months of age and **has not received scheduled immunizations** (especially Hib and pneumococcal vaccinations) or when the **immunization status cannot be determined**. Patients >12 months should have recognizable symptoms of bacterial meningitis.
- If a patient has been **pretreated with antibiotics**, because antibiotic treatment can mask the signs and symptoms of meningitis.

AAP Subcommittee on Febrile Seizures. Clinical practice guideline—febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics.* 2011;127(2):389–394.

124. Are EEG or neuroimaging studies indicated for a child with a simple febrile seizure?

No. An EEG done shortly after or within a month after a seizure does not predict either the recurrence of febrile seizures or the development of afebrile seizures/epilepsy in the ensuing 2 years. CT or MRI studies are not indicated because children who are neurologically healthy before a simple febrile seizure have a low likelihood of a clinically important intracranial structural abnormality.

AAP Subcommittee on Febrile Seizures. Clinical practice guideline—febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics.* 2011;127(2):389–394.

125. Do prolonged febrile seizures result in an increased peripheral or CSF white blood cell (WBC) count?

A common clinical question in children is whether a leukocytosis, if found, can be explained on the basis of a prolonged seizure as a stress reaction. In one study of 203 children with seizures and fever, 61% had a normal peripheral WBC count. No association was found between blood leukocytosis and febrile seizure duration in children. The febrile status epilepticus study (FEBSTAT) evaluated the CSF findings in 136 children with febrile status epilepticus in whom a nontraumatic LP was performed; 96% had <3 WBCs/mm^3.

Frank LM, Shinnar S, Hesdrofer DC, et al. Cerebrospinal fluid findings in children with fever associated status epilepticus: results of the consequences of prolonged febrile seizures (FEBSTAT) study. *J Pediatr.* 2012;161(6):1169–1171.
van Stuijvenberg M, Moll HA, Steyerberg EW, et al. The duration of febrile seizures and peripheral leukocytosis. *J Pediatr.* 1998;133(4):557–558.

126. What ancillary testing should be considered in a patient with a complex febrile seizure?

Most children with their **first complex febrile seizure** should undergo an LP for a CSF examination to rule out intracranial infection. Children with **focal motor seizures** or **postictal lateralized deficits** (motor paresis, unilateral sensory or visual loss, sustained eye deviation, or aphasia) should be *considered* for emergent neuroimaging to exclude a structural abnormality before the LP is done. An LP could result in cerebral herniation if ICP is increased because of a mass effect. However, if the patient is neurologically normal, data suggest an emergent CT may not be necessary. The immediate performance of an EEG offers limited insight into the patient's disease. Prominent generalized postictal slowing is not unexpected. Definite focal slowing suggests a possible structural abnormality. For a simple febrile seizure, an EEG is not indicated because it is not predictive of either the risk for recurrence of febrile seizures or the development of epilepsy.

Teng D, Dayan P, Tyler S, et al. Risk of intracranial pathologic conditions requiring emergency intervention after a first complex febrile seizure episode among children. *Pediatrics.* 2006;117(2):304–308.

DiMario FJ. Children presenting with complex febrile seizures do not routinely need computed tomography scanning in the emergency department. *Pediatrics.* 2006;117(2):528–530.

127. What is the risk for epilepsy after a simple febrile seizure?

The risk depends on several variables. In otherwise normal children with a simple febrile seizure, the risk for later epilepsy is about 2%. The risk for epilepsy is higher if any of the following is present:

- There is a close family history of nonfebrile seizures.
- Prior neurologic or developmental abnormalities exist.
- The patient had an atypical or complex febrile seizure, defined as focal seizures, seizures lasting at least 15 minutes, and/or multiple attacks within 24 hours.

One risk factor increases the risk to 3%. If all three risk factors are present, the likelihood of later epilepsy increases to 5% to 10%.

Smith DK, Sadler KP, Benedum M. Febrile seizures: risks, evaluation, and prognosis. *Am Fam Physician.* 2019;99(7):445–450.

Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. *N Engl J Med.* 1976;295(19):1029–1033.

KEY POINTS: FEBRILE SEIZURES

1. Simple: Brief and lasting $<$15 minutes
2. Complex: Focal, $>$15 minutes long, or recurrence within 24 hours
3. Risk for recurrent febrile seizure increases if positive family history or seizure occurs at $<$1 year of age and/or body temperature of $<$104°F (40°C)
4. Risk for developing future nonfebrile seizures is low (only 2% by age 7 years)
5. Normal long-term intellect and behavior compared with controls
6. Increased risk for developing epilepsy if complex febrile seizure, prior neurologic abnormality, or family history of seizure disorder

128. What is the long-term outcome for children with febrile seizures?

In a previously normal child, the risk for death, neurologic damage, or persistent cognitive impairment from a single benign febrile seizure is low. These potential complications are more likely with complex febrile seizures, but the risk is still exceedingly low. Impaired cognition in the latter group is more likely if afebrile seizures subsequently develop. Febrile status epilepticus has a very low mortality with proper treatment. However, the potential development of hippocampal injury (mesial temporal sclerosis) is currently being evaluated in the United States in the FEBSTAT study. The 1-year follow-up shows no significant cognitive impairment but shows a trend for receptive language and motor delay.

Weiss EF, Masur D, Shinnar S, et al. Cognitive functioning one month and one year following febrile status epilepticus. *Epilepsy Behav.* 2016;64(Pt A):283–288.

Scott RC. Consequences of febrile seizures in childhood. *Curr Opin Pediatr.* 2014;26(6):662–667.

Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. *N Engl J Med.* 1998;338(24):1723–1728.

129. After a febrile seizure, should a child be treated with prophylactic AEDs?

For most children, a simple febrile seizure is an unwanted but transient disruption of their health, and treatment is not necessary. Treatment interventions, either continuous or intermittent (at the time of fever), have been evaluated for valproate, pyridoxine, phenobarbital, phenytoin, diazepam, and clonazepam. Adverse effects were noted in up to 30% in the phenobarbital group (lower comprehension scores) and up to 36% in the benzodiazepine group. Long-term prophylaxis does not improve the prognosis in terms of subsequent epilepsy or motor or cognitive ability. In general, the side effects of prophylaxis (especially the hepatotoxicity and pancreatopathy associated with valproic acid therapy) outweigh the relatively minor risks of recurrence. Exceptions could include the very young child if febrile seizures recur frequently, children with preexisting neurologic abnormalities, or children with recurrent complex febrile seizures.

Offringa M, Newton R, Cozijnsen MA, Nevitt SJ. Prophylactic drug management for febrile seizures in children. *Cochrane Database Syst Rev.* 2017;2:CD003031.

130. Is the aggressive use of antipyretic therapy at the start of a febrile illness effective in reducing the likelihood of a febrile seizure?

Despite being recommended frequently by pediatricians, aggressive antipyretic use has not been shown to be effective in preventing recurrence of a febrile seizure.

Offringa M, Newton R, Cozijnsen MA, Nevitt SJ. Prophylactic drug management for febrile seizures in children. *Cochrane Database Syst Rev.* 2017;2:CD003031.
Strengell T, Uhari M, Tarkka R, et al. Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. *Arch Pediatr Adolesc Med.* 2009;163(9):799–804.

HEADACHE

131. What are the emergency priorities when evaluating a child with a severe headache?

As with all common presenting symptoms, the main priority is to rule out diagnostic possibilities that may be life threatening:

- Increased ICP (e.g., mass lesion, acute hydrocephalus)
- Intracranial infections (e.g., meningitis, encephalitis)
- Subarachnoid hemorrhage
- Stroke
- Malignant hypertension
- Acute angle closure glaucoma (may appear as a headache, but rare in children)

132. When should neuroimaging be considered in a child with headache?

- Abnormal neurologic signs (oculomotor abnormalities, gait ataxia, papilledema, focal weakness)
- Headache increasing in frequency and severity
- Headache occurring in early morning or awakening child from sleep
- Headache made worse by straining or by sneezing or coughing (may be a sign of increased ICP)
- Headache associated with severe vomiting without nausea
- Headache worsened or helped significantly by a change in position
- Macrocephaly
- Fall-off in linear growth rate
- Recent school failure or significant behavioral changes
- New-onset seizures, especially if seizure has a focal onset
- Migraine headache and seizure occurring in the same episode, with vascular symptoms preceding the seizure (20% to 50% risk for tumor or arteriovenous malformation)
- Cluster headaches in any child or teenager

Lewis DW, Ashwal S, Dahl G, et al. Practice parameter: evaluation of children and adolescents with recurrent headaches. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2002;59(4):490–498.
Medina LS, Pinter JD, Zurakowski D, et al. Children with headache: clinical predictors of space-occupying lesions and the role of neuroimaging. *Radiology.* 1997;202(3):819–824.

KEY POINTS: CLASSIC HEADACHE OF INCREASED INTRACRANIAL PRESSURE

1. Awakens patient from sleep at night
2. Pain present upon awakening in the morning
3. Vomiting without associated nausea
4. Made worse by straining, sneezing, or coughing
5. Intensity of pain changes with changes in body position
6. Pain lessens during the day

133. What are the three primary headache disorders in children?

These are recurrent headaches not attributable to underlying physical disease.

- **Migraine:** Most common type in children (4% in childhood, with a male predominance; after adolescence, more common in females)
- **Tension type:** Features different from migraine—bilateral, nonpulsating, not aggravated by activity; school problems with stress and absences and family dysfunction are frequently noted
- **Cluster:** Uncommon in childhood; consist of severe unilateral orbital or supraorbital pain with conjunctival injection and tearing

134. What are the clinical features of migraine headaches in children?

- *Migraine* is a periodic disorder with symptom-free periods characterized by headaches with a throbbing/pulsating nature, unilateral in older children and commonly bilateral in younger children, lasting 1 to 72 hours, with moderate or severe intensity, aggravated by routine physical activity and exercise, and associated with nausea and/or photophobia and phonophobia. There may be a history of recurrent vomiting, motion sickness, or vertigo. There is often a family history of migraine, and the genetics may be multifactorial.
- *Migraine with aura:* Previously called *classic migraine,* this is less common in children. The aura is a prodrome of variable focal neurologic features such as visual scotoma, sensory symptoms (numbness, tingling), sluggishness, and difficulty concentrating or motor features (weakness, dysphasia).
- *Migraine without aura:* Previously called *common migraine,* these are the more frequent type in childhood.

Other clinical syndromes that are considered migraine variants in childhood include cyclic vomiting syndrome; abdominal migraine; benign paroxysmal vertigo of childhood; and, possibly, infantile colic.

Guidetti V, Cerutti R, Faedda N, Natalucci G. Migraine in childhood: an organic, biobehavioral, or psychosomatic disorder? *Neurol Sci.* 2019;40(Suppl 1):93–98.

Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders. *Cephalalgia.* 2004;24(Suppl 1):1–160.

135. Which physical findings are important during the initial evaluation of possible migraine headache?

- **Height, weight, and head circumference** should be normal for age. Pituitary tumor, craniopharyngioma, and partial ornithine transcarbamylase deficiency may all result in growth failure and mimic migraine headache. Head circumference should be normal, ruling out hydrocephalus.
- **Skin** should be checked for abnormalities. Throbbing headaches are common in neurofibromatosis and systemic lupus erythematosus, both of which have easily recognizable skin manifestations.
- **Blood pressure** should be normal.
- Check for **sinus tenderness** or pain with sinus percussion or head movement (implying cervical spine disease). The patient should be examined for **carious teeth, misaligned bite, or disordered chewing and jaw opening** (temporomandibular joint dysfunction).
- **Auscultation** should reveal no cranial bruits (if present, these suggest possible arteriovenous malformation or mass lesion).
- The **neurologic examination**, including visual fields, should be normal.

Honig PJ, Charney EB. Children with brain tumor headaches: distinguishing features, *Am J Dis Child.* 1982;136(2):121–124.

136. When do children begin to have migraine headaches?

About 20% suffer their first headache before the age of 10 years.

Infantile migraine does occur. It often manifests as vomiting, pallor, vertigo, and ataxia, with or without headache, which can occur in a periodic fashion. These attacks frequently improve with sleep.

Barlow CF. Migraine in the infant and toddler. *J Child Neurol.* 1994;9(1):92–94.

137. Which foods have been associated with the development of migraine headaches?

Tyramine-rich foods (cheese, red wine), foods with monosodium glutamate (Asian food, adobo seasoning), nitrate-rich foods (smoked and lunch meats, salami), alcoholic beverages, caffeinated beverages, chocolate, citrus fruits, and sulfites (food coloring) have been associated with the development of migraine headaches.

138. What is familial hemiplegic migraine?

Familial hemiplegic migraine is an autosomal dominant disorder that is clinically characterized by transient hemiparesis and aphasia followed by migraine headache. About 20% are affected by progressive cerebellar ataxia. Mutations in *CACNA1A* (which encodes a neuronal calcium channel) on chromosome 19 are found in half of affected families.

Russell MB, Ducros A. Sporadic and familial hemiplegic migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management. *Lancet Neurol.* 2011;10(5):457–470.

139. What is the likely diagnosis for a 10-year-old girl with a normal neurologic examination but a history of headaches, a family history of migraines, and a presentation with 10 minutes of a spinning sensation and double vision followed by an occipital headache?

Basilar-type migraine, which occurs in 3% to 19% of childhood migraines, is a likely diagnosis. Symptoms related to balance, gait, and visual disturbance are followed by headache, which, unlike most migraines, is occipital. Patients with basilar artery migraine may have drop attacks with altered awareness. Syncope is also more common in patients with migraine compared with the general population.

Chou IC, Lee IC, Hong SY. Basilar-type migraine: an overlooked cause of loss of consciousness in pediatric emergency rooms. *Pediatr Neonatol.* 2018;59(3):315–316.

140. How do the triptans work to treat an acute migraine headache?

Triptans are serotonin receptor subtype-selective drugs, which were thought initially to work primarily through their vasoconstrictive effects on arterial smooth muscle in cranial blood vessels. However, there are questions whether the primary mechanism is central or peripheral. Triptans act on peripheral nerve endings, preventing the release of proinflammatory and vasoactive peptides, including substance P and calcitonin gene-related peptide (GCRP). Also unclear is the apparent selectivity of triptans for migraine pain but not other kinds of somatic pain.

Cameron C, Kelly S, Hsieh SC, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. *Headache.* 2015;55(Suppl 4):221–235.

Pringsheim T, Becker WJ. Triptans for symptomatic treatment of migraine headache. *BMJ.* 2014;348:g2285.

141. What nonpharmacologic therapies are available for the prevention of migraine?

- Migraine elimination diet
- Vitamin therapy: riboflavin, coenzyme Q10, magnesium
- Normalization of sleep habits
- Discontinuance of possible triggering medications (e.g., analgesic overuse, bronchodilators, oral contraceptives)
- Biofeedback
- Relaxation therapy
- Family counseling (if family stress is a trigger)
- Self-hypnosis

Nicholson RA, Buse DC, Andrasik F, Lipton RB. Nonpharmacologic treatments for migraine and tension-type headache: how to choose and when to use. *Curr Treat Options Neurol.* 2011;13(1):28–40.

142. What categories of medication are available for the prevention of migraine in children?

As with many therapies used for children, most studies involve adults with extrapolation to children for whom the medications may not work as well. These medications are regularly used by clinicians, but are not yet approved by the U.S. FDA for children. Keys to therapy are gradually increasing the dose until effectiveness is or is not established or adverse effects intervene.

- Antidepressants (e.g., tricyclics such as amitriptyline)
- Antihistamine (e.g., cyproheptadine, which has antiserotonergic effects)
- Antihypertensives (e.g., beta-blockers such as propranolol and calcium channel blockers)
- Anticonvulsants (including divalproex sodium and topiramate)
- Nutraceuticals (e.g., riboflavin)

Hickman C, Lewis KS, Little R, et al. Prevention for pediatric and adolescent migraine. *Headache.* 2015;55(10):1371–1381.

El-Chammas K, Keyes J, Thompson N, et al. Pharmacologic treatment of pediatric headaches: a meta-analysis. *JAMA Pediatr.* 2013;167(3):250–258.

143. Who should be started on prophylactic medication for migraine headaches?

There are no precise criteria, but generally prophylactic treatment should be considered if any of the following are present:

- Headaches with aura occur frequently.
- Headaches with aura are poorly responsive to abortive medication.
- School attendance is significantly affected.
- Headaches, although infrequent, last for several days.

144. How long are the prophylactic medications continued?

The optimal duration of therapy remains unclear, but many authorities suggest a treatment duration of 3 to 6 months followed by an attempt at weaning. Less than 50% will require the reinitiation of medication.

145. What distinguishes tension-type headaches from migraines?

Unlike migraines, these headaches are bilateral with a pressing and tightening quality (as opposed to the pulsatile quality of migraines) and usually of mild or moderate intensity. They are not associated with nausea or vomiting and typically not worsened by light or sound. Pericranial muscle tenderness is common. Psychological stress is associated with and can aggravate tension-type headaches. Activation of hyperexcitable peripheral afferent neurons from head and neck muscles, as well as abnormalities in central pain processing and pain sensitivity, likely contributes to the problem.

Loder E, Rizzoli R. Tension-type headache. *BMJ.* 2008;336(7635):88–92.

MOVEMENT DISORDERS

146. What are the various types of pathologic hyperkinetic movements?

- **Tremors:** Rhythmic oscillatory movements, both supination-pronation and flexion-extension, seen in resting state or with activity
- **Chorea:** Quick dancing movements of proximal and distal muscles with irregular, unpredictable random jerks
- **Athetosis:** Irregular, slow, distal writhing movements
- **Stereotypy:** Repetitive, purposeless motions (e.g., body rocking, head rolling) that resemble voluntary movements often associated with akathisia (sensory and motor restlessness); often seen in autism spectrum disorders
- **Dystonia:** Slow, twisting, sustained movements; may result in abnormal postures and progress to contractures
- **Ballismus:** Abrupt, random, violent, flinging movements, often proximal and unilateral
- **Myoclonus:** Abrupt, brief, jerky contractions of one or more muscles, often stimulus sensitive
- **Tics:** Rapid, sudden, repetitive movements or vocalizations

147. What techniques can be used to elicit abnormal movements (particularly chorea)?

Methods of *provocative testing* include the maintenance of posture in extension against gravity, hyperpronation (or "spooning," especially above the head), tongue protrusion ("trombone tongue"), squeezing the finger of the examiner ("milkmaid's grip"), pouring liquid, and drawing a spiral.

148. What disorders are commonly associated with the various hyperkinetic movements?

- **Tremors, resting:** primary juvenile Parkinson disease, secondary Parkinson disease
- **Tremors, kinetic:** essential (familial) tremor, cerebellar disorders, brainstem tumors, hyperthyroidism, Wilson disease, electrolyte disturbance (e.g., glucose, calcium, magnesium), heavy-metal intoxication (e.g., lead, mercury), multiple sclerosis
- **Chorea:** Sydenham chorea (associated with rheumatic fever), Huntington disease, hyperthyroidism, infectious mononucleosis, pregnancy, anticonvulsants, neuroleptic drugs, closed head injury, systemic lupus erythematosus, carbon monoxide poisoning, Wilson disease, hypocalcemia, polycythemia, parainfectious and infectious encephalopathies (e.g., rubeola, syphilis)
- **Athetosis:** cerebral palsy, other static encephalopathies, Lesch-Nyhan syndrome, kernicterus
- **Stereotypy:** autism, Rett syndrome, neuroleptic drugs (i.e., tardive dyskinesia), schizophrenia
- **Dystonia:** idiopathic primary dystonias (e.g., torsion dystonia), Sandifer syndrome, spasmus nutans, neuroleptic drugs, static encephalopathy, perinatal asphyxia, familial dystonia (sometimes dopa-responsive)
- **Ballismus:** encephalitis, closed head injury
- **Myoclonus:** sleep myoclonus, benign myoclonus of infancy, postanoxic encephalopathy, uremic encephalopathy, hyperthyroidism, urea cycle defects, side effects of tricyclic therapy, slow virus infections, Wilson disease, myoclonus-opsoclonus, neuroblastoma, epileptic encephalopathies, mitochondrial disease, prion disease, Tay-Sachs disease, startle disease, sialidosis

149. What constitutes a tic?

Tics are brief, sudden, repetitive, stereotyped, involuntary, and purposeless movements or vocalizations. They most commonly involve muscles of the head, neck, and respiratory tract. Their frequency can be increased by anxiety, stress, excitement, and fatigue. They are decreased during sleep and relaxation; during activities involving

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high concentration; and, at times, through voluntary action. In some cases, premonitory feelings (e.g., irritation, tickle, temperature change) can precipitate the motor or vocal response.

150. What is the range of clinical tics?

- **Motor (simple clonic):** eye blinking, eye deviation, head twitching, shoulder shrugging
- **Motor (simple dystonic):** bruxism, abdominal tensing, shoulder rotation
- **Motor (complex):** grunting, barking, sniffing, snorting, throat clearing, spitting
- **Vocal (complex):** coprolalia (obscene words), echolalia (repeating another's words), palilalia (rapidly repeating one's own words)

151. What are the causes of a tic?

Transient and chronic tic disorders usually do not have an identifiable cause. However, dyskinesias such as tics can be found in association with a number of other conditions:

- **Chromosomal abnormalities:** Down syndrome, fragile X syndrome
- **Developmental syndromes:** autism, pervasive developmental disorder, Rett syndrome
- **Drugs:** anticonvulsants, stimulants (e.g., amphetamines, cocaine, methylphenidate, pemoline)
- **Infections:** encephalitis, postrubella syndrome

152. How should simple tics be treated?

Simple motor tics are common and occur in more than 5% to 21% of school-age children. Simple tics generally do not require pharmacologic intervention and can be treated expectantly by developing relaxation techniques, minimizing stresses that exacerbate the problem, avoiding punishment for tics, and decreasing fixation on the problem. Most simple tics self-resolve in 2 to 12 months. Moderate or severe tics, especially when significant patient distress is involved, may warrant pharmacologic treatment.

153. What comorbidities occur in children with tics?

The prevalence of tic disorder is higher in younger children and in males and is associated with school dysfunction, learning disabilities, obsessive-compulsive disorder, and ADHD. In addition, separation anxiety, overanxious disorder, simple phobia, social phobia, agoraphobia, mania, major depression, and oppositional defiant disorder were found to be significantly more common in children with tics.

154. When do tics warrant pharmacologic intervention?

Tics that have a significant disabling impact on a child's educational, social, or psychological well-being (particularly if they have been present for >1 year) may require intervention. When the complexity of tics increases or the diagnosis of Tourette syndrome is suspected, pharmacotherapy should also be considered. Most theories point to a hyper-dopaminergic state of the basal ganglia as the most likely etiology for unregulated movements. Pharmacologic management includes α_2-agonists (e.g., clonidine, guanfacine) or the administration of atypical neuroleptics (e.g., risperidone, haloperidol) and/or the cessation of any stimulant drugs that can cause dopamine release. Because of the high associated incidence of obsessive-compulsive disorder and ADHD, other medications may be needed, and consultation with a pediatric psychiatrist or neurologist is often warranted.

155. What are the diagnostic criteria for Tourette syndrome?

In 1885, Gilles de la Tourette described a syndrome of motor tics and vocal tics with behavioral disturbances and a chronic and variable course. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria for Tourette syndrome require the following:

- Two or more motor tics *and* at least one vocal tic
- Presence of tics for more than 1 year (usually on a daily basis, but can be intermittent)
- Onset before the age of 18 years
- Not caused by medications or any identifiable medical etiology

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American Psychiatric Association. *Diagnosis and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013.

156. What is coprolalia?

Coprolalia is an irresistible urge to utter profanities, occurring as a phonic tic. Only 20% to 40% of patients with Tourette syndrome have this phenomenon, and it is not essential for the diagnosis.

157. What behavioral problems are associated with Tourette syndrome?

- Obsessive-compulsive disorder
- ADHD
- Severe conduct disorders
- Learning disabilities (particularly math)
- Sleep abnormalities
- Depression, anxiety, and emotional lability

Tourette Syndrome Association. www.tsa-usa.org. Accessed January 22, 2020.
Hallett M. Tourette syndrome: update. *Brain* 2015;37(7):651–655.

158. Why is the diagnosis of Tourette syndrome commonly delayed?

- Tendency to associate unusual symptoms with attention-getting or psychological problems
- Incorrect belief that all children with Tourette syndrome must have severe tics
- Attribution of vocal tics to upper respiratory infections, allergies, or sinus or bronchial problems
- Diagnosis of eye blinking or ocular tics as ophthalmologic problems
- Mistaken belief that coprolalia is an essential diagnostic feature

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Singer HS. Tic disorders. *Pediatr Ann.* 1993;22(1):22–29.

159. What is the cause of tardive dyskinesia?

Tardive dyskinesia is a hyperkinetic disorder of abnormal movements, most commonly involving the face (e.g., lip smacking or pursing, chewing, grimacing, tongue protruding). Tardive dyskinesia occurs during treatment with neuroleptics (e.g., chlorpromazine, haloperidol, metoclopramide) or within 6 months of their discontinuance. This disorder is thought to be a result of dopaminergic dysfunction of the basal ganglia because these drugs act as dopamine-receptor blockers.

160. For a patient taking neuroleptic medication, how long must therapy last before symptoms of tardive dyskinesia can develop?

About 3 months of continuous or intermittent treatment with neuroleptics is needed before the risk for tardive dyskinesia increases.

161. What is neuroleptic malignant syndrome?

Neuroleptic malignant syndrome is a syndrome of movement (rigidity, tremor, chorea, and dystonia), autonomic dysfunction (fever, hypertension, tachycardia, diaphoresis, irregular respiratory pattern, urinary retention), alteration of consciousness, and rhabdomyolysis with an elevation of creatinine kinase. It occurs within weeks of starting neuroleptics, and there is a 20% associated mortality rate in adults.

162. Which movement disorder in children presents with “dancing eyes and dancing feet”?

Opsoclonus-myoclonus *(infantile polymyoclonus syndrome* or *acute myoclonic encephalopathy of infants)* is a rare but distinctive movement disorder in children that is seen during the first 1 to 3 years of life. Opsoclonus is characterized by wild, chaotic, fluttering, irregular, rapid, conjugate bursts of eye movements (saccadomania). Myoclonus is sudden, shock-like muscular twitches of the face, limbs, or trunk. The anatomic site of pathology is the cerebellar outflow tracts. The etiology may be direct viral invasion, postinfectious encephalopathy, or neuroblastoma. Immunomodulatory therapy with corticosteroids (ACTH, dexamethasone), intravenous immunoglobulin (IVIG), and rituximab may be useful.

NEONATAL SEIZURES

163. How are neonatal seizures classified?

Although there is no universally accepted standard classification system, one based on clinical criteria is commonly used, primarily based on motoric manifestations. It divides neonatal seizures into four types:

- **Subtle**: ocular phenomena, oro-buccal-lingual movements, limb bicycling, autonomic phenomena, apneic seizures
- **Tonic** (focal or generalized): stiffening; may be confused with decerebrate posturing
- **Clonic** (focal or multifocal): localized rhythmic jerks of face, limb, or trunk or more generalized rhythmic jerking, usually in a non-Jacksonian fashion
- **Myoclonic** (focal, multifocal, or generalized): rapid, single or arrhythmic repetitive jerks of limb or entire body; can mimic the Moro (startle) reflex

All seizure types are recognized as paroxysmal alterations in behavioral, motor, or autonomic function. Not all clinically observed phenomena, however, are accompanied by associated epileptic surface-EEG activity, and this electroclinical disassociation is increased after AED treatment. Partial clonic, tonic, and myoclonic seizures have been shown to have the most consistent EEG ictal correlate. Of note, a large percentage of neonates who have undergone an antenatal or postnatal insult and/or are critically ill may have *subclinical seizures,* which are manifest only on EEGs.

164. Why are generalized seizures uncommon in newborns?

Generalized seizures are rarely seen in neonates because of **incomplete myelination**, which tends to prevent highly organized, synchronized ictal motor activity from occurring.

165. What is the most common type of clinical seizure during the neonatal period?

The so-called **subtle seizure** is the most common. Rather than arising as an abrupt dramatic “convulsion” with obvious forceful twitching or posturing of the muscles, the subtle seizure appears as unnatural, repetitive, stereotyped choreography, featuring oral-buccal-lingual movements (e.g., sucking, lip smacking, chewing, tongue protrusion), eye blinking, nystagmus, or complex integrated limb movements (swimming, pedaling, or rowing) and other fragments of activity drawn from the limited repertoire of normal infant activity. Apnea may also be a feature of a subtle seizure.

166. What is the most common cause of neonatal seizures?

Hypoxic-ischemic encephalopathy with seizures beginning on the first day of life. Neonatal stroke is another frequent cause of seizure in the first days of life. Other causes of neonatal seizures include intracranial hemorrhage; infectious meningitis or encephalitis; and transient metabolic disturbances such as hypoglycemia, hyponatremia, and hypocalcemia. Inborn errors of metabolism and congenital anomalies of brain development are less common causes of seizures. With advancements in genetic testing, neonatal epilepsy syndromes (without structural brain abnormalities) are increasingly being recognized as a cause of neonatal seizures.

Rennie JM, de Vries LS, Blennow M, et al. Characterization of neonatal seizures and their treatment using continuous EEG monitoring: a multicentre experience. *Arch Dis Child Fetal Neonatal Ed.* 2018;F1–F9:10.1136.
Shellhaas RA, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: characteristics of a prospective US cohort. *Neurology.* 2017;89(9):893–899.
Glass HC. Neonatal seizures: advances in mechanisms and management. *Clin Perinatol.* 2014;41(1):177–190.

167. What are other causes of neonatal seizures?

- Infection
- Toxins (e.g., inadvertent fetal injection with local anesthetic; cocaine, including withdrawal)
- Metabolic abnormalities (e.g., hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency, inborn errors)
- CNS malformations
- Cerebrovascular lesions (e.g., intraventricular, periventricular hemorrhage, subarachnoid hemorrhage, infarction, arterial cerebral occlusion)
- Benign familial neonatal-infantile seizures (e.g., a sodium channelopathy)

Shellhaas RS, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: characteristics of a prospective US cohort. *Neurology.* 2017;89(9):893–899.
Glass HC. Neonatal seizures: advances in mechanisms and management. *Clin Perinatol.* 2014;41(1):177–190.
Zupanc ML. Neonatal seizures. *Pediatr Clin North Am.* 2004;51(4):961–978.

168. In premature and full-term infants, how do the causes of seizures vary with regard to relative frequency and time of onset?

See Table 13.4.

Table 13.4 Variance in Relative Frequency and Time of Onset of Causes of Seizures

	Postnatal Time of Onset		***Relative Frequency***	
ETIOLOGY	**0-3 DAYS**	**>3 DAYS**	**PREMATURE**	**FULL-TERM**
Hypoxic-ischemic	+		+++	+++
Intracranial hemorrhage[*]	+	+	++	+
Hypoglycemia	+		+	+
Hypocalcemia	+	+	+	+
Intracranial infection[†]	+	+	++	+
Developmental defects	+	+	++	++
Drug withdrawal	+	+	+	+

[*] Hemorrhages are principally germinal matrix-intraventricular in the premature infant and subarachnoid or subdural in the term infant.
[†] Early seizures occur usually after intrauterine nonbacterial infections (e.g., toxoplasmosis, cytomegalovirus infection), and later seizures usually occur with herpes simplex encephalitis or bacterial meningitis.
Adapted from Volpe JJ, ed. *Neurology of the Newborn.* 3rd ed. Philadelphia, PA: W.B. Saunders; 1995:184.

169. What is an acceptable workup in a newborn with seizures?

- A careful prenatal and natal history and a complete physical examination are needed.
- Laboratory studies should include blood for glucose, electrolytes, calcium, phosphorus, and magnesium.
- An LP should be performed to rule out meningitis.
- Neuroimaging studies (cranial ultrasound, CT scan, or, preferably, MRI) are mandatory.

- Additional studies may include blood levels for ammonia, lactate, and pyruvate; additional CSF studies (e.g., lactate, pyruvate, glucose, glycine, CSF neurotransmitters if metabolic disease is suspected); and urine studies for organic and amino acid analysis for possible inborn errors of metabolism.
- Serial use of EEGs can document persistent seizures, especially the persistence of electrographic seizures without clinical seizures after initial treatment.

170. In what settings should an inborn error of metabolism be suspected as a cause of neonatal seizures?

- The onset of seizures is beyond day 1 of life. (An exception is pyridoxine-dependent epilepsy, which can occur on day 1 of life; patients may have a history of seizures in utero.)
- The infant becomes symptomatic after the introduction of enteral or parenteral nutrition.
- The seizures are intractable and do not respond to conventional AEDs.
- Characteristic EEG patterns may be seen in maple syrup urine disease, propionic acidemia, and pyridoxine-dependent epilepsy.

Scher MS. Neonatal seizures. In Polin RA, Yoder MC, eds. *Workbook in Practical Neonatology*. 4th ed. Philadelphia, PA: Saunders Elsevier; 2007:363.

171. How are seizures differentiated from tremors in the neonate?

See Table 13.5.

Table 13.5 Tremors Versus Seizures

CLINICAL FEATURE	TREMORS	SEIZURES
Suppressibility	+	0
Abnormality of gaze or eye movement	0	+
Movements are exquisitely stimulus sensitive	+	0
Predominant movement	Tremor	Clonic jerking
Movements cease with passive flexion	+	0
Autonomic changes	0	+

172. How should neonatal seizures be managed?

As with seizures in older children, airway management and cardiovascular support of the neonate are primary. It is critical to be certain that the cause of a neonatal seizure is not a correctable metabolic problem (e.g., hypoglycemia, hypocalcemia, hypomagnesemia) or a CNS infection. An inborn error of metabolism should be suspected if seizures begin after feeding.

If antiseizure medication is felt to be warranted, **phenobarbital** is typically the *first-line therapy* at an initial dose of 15 to 20 mg/kg IV followed by a maintenance dose of 3 to 6 mg/kg day. Repeat boluses of 5 mg/kg can be given every 15 to 30 minutes (to a maximum total of 30 to 40 mg/kg) for persistent seizures, with the goal of a phenobarbital level in the therapeutic range of 15 to 40 mcg/mL. In the setting of seizures refractory to phenobarbital and a second medication (or for use as a second medication), a benzodiazepine (e.g., lorazepam or midazolam) can be utilized. For seizures resistant to antiepileptic medication, consider the possibility of a pyridoxine-dependent seizure, which will stop within minutes after an IV dose of 100 mg of pyridoxine.

Second choice medications for persistence of seizures vary by institution and local custom, as data in neonates are limited. Fosphenytoin is a common second choice and is generally preferred over phenytoin. Use of phenytoin can be problematic due to a variable rate of hepatic metabolism and poor enteral absorption in neonates. Levetiracetam and topiramate appear to be as efficacious as older agents and with more favorable safety profiles. Bumetanide, a loop-diuretic, was thought to be a possible add-on option to phenobarbital for treatment of neonatal seizures but failed an open-label trial for efficacy and was associated with an increased risk for hearing loss.

Of note, efficacy even with two agents is low, with only one-third of patients showing an immediate complete response. Even after apparently successful IV treatment with phenobarbital and fosphenytoin with the resolution of clinical seizures, electrographic seizures may continue unabated. The significance of this finding is unclear, and the need to suppress electrographic seizures without clinical accompaniments is controversial.

Ahrens S, Ream MA, Slaughter LA. Status epilepticus in the neonate: update in treatment strategies. *Curr Treat Options Neurol.* 2019;21(2):8.

El-Dib M, Soul JS. The use of phenobarbital and other anti-seizure drugs in newborns. *Semin Fetal Neonatal Med.* 2017;22(5):321–327.

173. When is treatment with pyridoxine effective in neonatal seizures?

Seizures are a common manifestation of inborn errors of metabolism. Pyridoxine (vitamin B_6) is an important cofactor in the synthesis of the inhibitory neurotransmitter GABA. Some genetic disorders are associated with **pyridoxine-dependent epilepsy**. One involves a defect in the *ALDH7A1* gene, which codes for the enzyme α-aminoadipic semialdehyde dehydrogenase (also known as *antiquitin*), which is involved in the breakdown of CNS lysine. Another is pyridoxal-5'-phosphate oxidase (PNPO) deficiency. PNPO converts pyridoxine to its active ingredient. Pipecolic acid is elevated in pyridoxine-dependent epilepsy. Pyridoxine-dependent epilepsy should be considered in neonates with medically refractory seizures.

Szymańska K, Kuśmierska, Demkow U. Inherited disorders of brain neurotransmitters: pathogenesis and diagnostic approach. *Adv Exp Med Biol.* 2015;837:1–8.
Plecko B. Pyridoxine and pyridoxalphosphate-dependent epilepsies. *Handb Clin Neurol.* 2013;113:1811–1817.

174. What is the treatment for benign familial neonatal seizures?

Benign familial neonatal seizures are a neonatal-onset epilepsy with characteristic focal seizures of asymmetric tonic posturing (alternating from side to side), apnea, and oxygen desaturation. These have been associated with mutations in the potassium channel, especially the *KCNQ2* and *KCNQ3* genes. There is typically an excellent response to either carbamazepine or oxcarbazepine.

Sands TT, Ballestri M, Bellini G, et al. Rapid and safe response to low-dose carbamazepine in neonatal epilepsy. *Epilepsia.* 2016;57(12):2019–2030.

175. Of what prognostic value is the interictal EEG in a neonate with seizures?

This study can have significant prognostic value. Severe interictal EEG abnormalities (e.g., burst suppression, marked voltage suppression, flat or isoelectric) are highly predictive (90%) of a fatal outcome or severe neurologic sequelae. Conversely, a normal interictal EEG in a term infant with seizures confers a very low (10%) likelihood of significant neurologic impairment. Moderate abnormalities (e.g., voltage asymmetries, immature patterns) have a mixed outcome.

Laroia N, Guillet R, Burchfiel J, McBride MC. EEG background as predictor of electrographic seizures in high risk neonates. *Epilepsia.* 1998;39(5):545–551.

176. After an infant has recovered from a seizure, how long should medication be continued?

There are no clear guidelines for the duration of therapy after neonatal seizures. Maintenance therapy typically involves the use of phenobarbital because it is difficult to achieve therapeutic levels of phenytoin with oral administration in infancy, and others are less well studied. Although phenobarbital is generally well tolerated, it may have deleterious effects on behavior, attention span, and possibly brain development. It does not prevent the later development of epilepsy. Many authorities recommend discontinuing therapy if the neurologic examination has normalized. In addition, if the neurologic examination is abnormal but an EEG by the age of 3 months reveals no seizure activity, consideration can also be given to stopping phenobarbital.

177. In patients with neonatal seizures, how does the cause affect the prognosis?

See Table 13.6.

Table 13.6 Relationship Between Cause and Prognosis of Neonatal Seizure

ETIOLOGY	FAVORABLE OUTCOME*	MIXED OUTCOME	UNFAVORABLE OUTCOME*
Toxic-metabolic	Simple late-onset hypocalcemia Hypomagnesemia Hyponatremia Mepivacaine toxicity	Hypoglycemia Early-onset complicated hypocalcemia Pyridoxine dependency	Some aminoacidurias
Asphyxia	—	Mild hypoxic-ischemic encephalopathy	Severe hypoxic-ischemic encephalopathy
Hemorrhage	Uncomplicated subarachnoid hemorrhage	Subdural hematoma Intraventricular hemorrhage (grades I and II)	Intraventricular hemorrhage (grades III and IV)

Continued on following page

Table 13.6 Relationship Between Cause and Prognosis of Neonatal Seizure (*Continued*)

ETIOLOGY	FAVORABLE OUTCOME	MIXED OUTCOME	UNFAVORABLE OUTCOME
Infection	—	Aseptic meningoencephalitis; some bacterial meningitides	Herpes simplex encephalitis; some bacterial meningitides
Structural	—	Simple traumatic contusion	Malformations of the central nervous system

[*] Favorable prognosis implies at least an 85% to 90% chance of survival and subsequent normal development. Unfavorable prognosis implies a high likelihood (85% to 90%) of death or serious handicap in survivors.

From Scher MS. Neonatal seizures. In Polin RA, Yoder MC, eds. *Workbook in Practical Neonatology.* 4th ed. Philadelphia, PA: Saunders Elsevier; 2007:370.

NEUROCUTANEOUS SYNDROMES

178. What are the three most common neurocutaneous syndromes?

Neurocutaneous syndromes (also called *phakomatoses*) are disorders characterized by the presence of tumors in various parts of the body (including the ocular and central nervous systems) and characteristic dermatologic findings of varying severity. The three most common are:

- Neurofibromatosis
- Tuberous sclerosis complex
- Sturge-Weber syndrome

179. What are the inheritance patterns of the various neurocutaneous syndromes?

- **Neurofibromatosis:** Autosomal dominant
- **Tuberous sclerosis complex:** Autosomal dominant
- **von Hippel-Lindau syndrome:** Autosomal dominant
- **Incontinentia pigmenti:** X-linked dominant
- **Sturge-Weber syndrome:** Sporadic
- **Klippel-Trénaunay-Weber syndrome:** Sporadic

180. What are the diagnostic criteria for neurofibromatosis-1 (NF1)?

Two or more of the following:

- Café au lait spots (six or more that are >0.5 cm in diameter before puberty; six or more that are >1.5 cm in diameter after puberty)
- Skinfold freckling (axillary or inguinal region)
- Neurofibromas (two or more) of any type, or at least one plexiform neurofibroma
- Iris hamartomas, also called *Lisch nodules* (two or more)
- Characteristic osseous lesion (i.e., sphenoid dysplasia, thinning of the cortex of the long bones with or without pseudoarthrosis)
- First-degree relative with NF1 diagnosed by the previous criteria

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Williams VC, Lucas J, Babcock MA, et al. Neurofibromatosis type 1 revisited. *Pediatrics.* 2009;123(1):124–133.

181. How does NF1 differ from NF2?

NF1, which is also known as *classic von Recklinghausen disease,* is much more common (1 in every 3000 to 4000 births) than NF2 and accounts for up to 90% of cases of neurofibromatosis. NF2 (1 in every 50,000 births) is characterized by bilateral acoustic neuromas, intracranial and intraspinal tumors, and affected first-degree relatives. NF1 has been linked to alterations on chromosome 17, whereas NF2 is linked to alterations on chromosome 22. Dermatologic findings and peripheral neuromas are rare in NF2. Other, rarer subtypes of neurofibromatoses (e.g., segmental distribution) have been described.

Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. *Lancet.* 2009;373(9679):1974–1986.

182. How common are café au lait spots at birth?

Up to 2% of black infants will have three café au lait spots at birth, whereas one café au lait spot occurs in only 0.3% of white infants. White infants with multiple café au lait spots at birth are more likely than black infants to develop neurofibromatosis. In older children, a single café au lait spot that is more than 5 mm in diameter can be found in 10% of white and 25% of black children.

Hurwitz S. Neurofibromatosis. In Hurwitz S, ed. *Clinical Pediatric Dermatology.* 2nd ed. Philadelphia, PA: W.B. Saunders; 1993:624–629.

183. If a 2-year-old child has seven café au lait spots that are larger than 5 mm in diameter, what is the likelihood that neurofibromatosis will develop, and how will it evolve?

Up to 75% of these children, if followed sequentially, will develop one of the varieties of neurofibromatosis, most commonly type 1. In a study of nearly 1900 patients, 46% with sporadic NF1 did not meet criteria by the age of 1 year. By the age of 8 years, however, 97% met the criteria, and by the age of 20 years, 100% did. The typical order of appearance of features is café au lait spots, axillary freckling, Lisch nodules, and neurofibromas. Yearly evaluation of patients with suspicious findings should include a careful skin examination, ophthalmologic evaluation, and blood pressure measurement.

DeBella K, Szudek J, Friedman JM. Use of the National Institutes of Health criteria for the diagnosis of neurofibromatosis 1 in children. *Pediatrics.* 2000;105(3 Pt 1):608–614.

Korf BR. Diagnostic outcome in children with multiple café-au-lait spots. *Pediatrics.* 1992;90(6):924–927.

184. What are Lisch nodules?

Pigmented iris hamartomas (Fig. 13.5). Although these are not usually present at birth in patients with NF1, up to 90% will develop multiple Lisch nodules by the age of 6 years. Hamartomas are focal malformations that are microscopically composed of multiple tissue types, and these can resemble neoplasms. However, unlike neoplasms, they grow at similar rates as normal components and are unlikely to pathologically compress adjacent tissue.

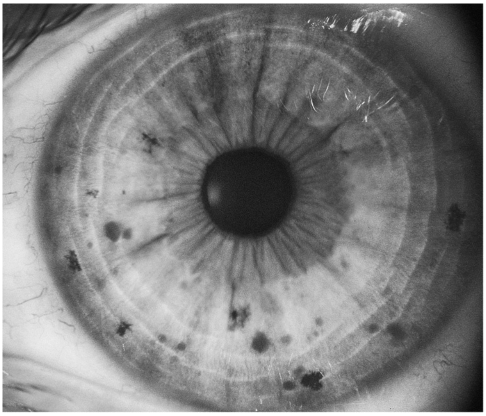

Fig. 13.5 Pigmented iris hamartomas (Lisch nodules). (From Habif TP, ed. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 5th ed. Philadelphia, PA: Elsevier; 2010: 985.)

185. How common is a positive family history in cases of NF1?

Because of the high spontaneous mutation rate for this autosomal dominant disease, only about **50%** of newly diagnosed cases are associated with a positive family history.

186. What are the primary diagnostic criteria for tuberous sclerosis complex (TSC)?

TSC is characterized by hamartomatous growths that occur in multiple tissues. The National Institutes of Health Consensus Conference in 1998 revised the diagnostic criteria for TSC on the basis of major or minor features. Definite TSC consisted of two major features or one major and two minor features; probable and possible TSC had fewer features (Table 13.7). No single finding was considered pathognomonic for TSC. Two gene site abnormalities, *TSC1* (chromosome 9) and *TSC2* (chromosome 16), have been identified. Genetic testing is now available.

Randle SC. Tuberous sclerosis complex: a review. *Pediatr Ann.* 2017;46(4):e166–e171.

Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med.* 2006;355(13):1345–1356.

Table 13.7 Diagnostic Features for Tuberous Sclerosis Complex

MAJOR FEATURES	MINOR FEATURES
Facial angiofibromas	Dental enamel pits
Nontraumatic ungual or periungual fibroma	Bone cysts

Continued on following page

Table 13.7 Diagnostic Features for Tuberous Sclerosis Complex (*Continued*)

MAJOR FEATURES	MINOR FEATURES
Hypomelanotic macules (>3)	Hamartomatous rectal polyps
Shagreen patch	Gingival fibromas
Multiple retinal nodular hamartomas	Cerebral white matter migration tracts
Cortical tuber	
Subependymal nodule or giant cell astrocytoma	
Cardiac rhabdomyoma, single or multiple	

187. What is the classic triad of TSC?

- **Seizures**
- **Mental retardation**
- **Facial angiofibroma (adenoma sebaceum)**

However, less than one-third of patients will develop these classic features.

Staley BA, Vail EA, Thiele EA. Tuberous sclerosis complex: diagnostic challenges, presenting symptoms, and commonly missed signs. *Pediatrics.* 2011;127(1):e117–e125.

188. What is the most common presenting symptom of TSC?

Seizures. About 85% of patients have seizures, and epileptic (previously called infantile) spasms are the most common. The first-line treatment of epileptic spasms in TSC is vigabatrin (as opposed to ACTH for other etiologies of epileptic spasm). Tonic and atonic seizures are also seen. Complex partial seizures are frequently seen in conjunction with other seizure types. Mental retardation is especially common with the onset of seizures before the age of 2 years. Autism and other behavioral disturbances are also frequently seen in children with TSC.

Randle SC. Tuberous sclerosis complex: a review. *Pediatr Ann.* 2017;46(4):e166–e171.
Staley BA, Vail EA, Thiele EA. Tuberous sclerosis complex: diagnostic challenges, presenting symptoms, and commonly missed signs. *Pediatrics.* 2011;127(1):e117–e125.

189. What are skin findings in patients with tuberous sclerosis?

See Table 13.8.

Table 13.8 Skin Findings in Tuberous Sclerosis

AGE AT ONSET	SKIN FINDINGS	INCIDENCE (%)
Birth or later	Hypopigmented macules	80
2-5 yr	Angiofibromas	70
2-5 yr	Shagreen patches	35
Puberty	Periungual and gingival fibromas	20-50
Birth or later	Café au lait spots	25

190. Why is the term *adenoma sebaceum* a misnomer when used to describe patients with tuberous sclerosis?

On biopsy, these papules are actually **angiofibromas**. They have no connection to sebaceous units or adenomas. This rash occurs in about 75% of patients with tuberous sclerosis, usually developing on the nose and central face between the ages of 5 and 13 years. It is red, papular, and monomorphous, and it is often mistaken for acne (Fig. 13.6). The diagnosis of tuberous sclerosis should be entertained in children who develop a rash that is suggestive of acne well before puberty.

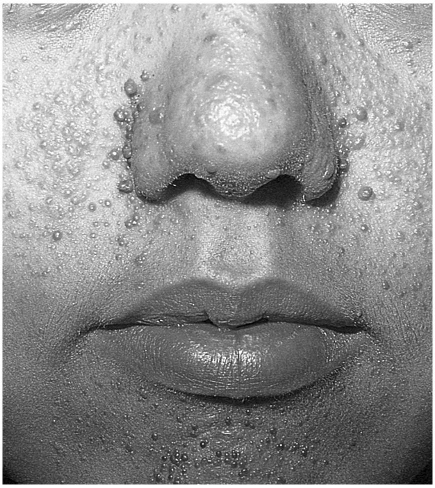

Fig. 13.6 Adenoma sebaceum in a patient with tuberous sclerosis. These angiofibromas first appear as flat, pink macules and later become papular. Lesions may bleed easily. (From Habif TP. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 5th ed. Philadelphia, PA: Elsevier; 2010:988.)

191. What is the "tuber" of tuberous sclerosis?

These 1- to 2-cm lesions consist of small stellate neurons and astroglial elements that are thought to be primitive cell lines resulting from abnormal differentiation. They may be located in various cortical regions. They are firm to the touch, like a small potato or tuber.

192. What is the tissue type of a shagreen patch?

A shagreen patch is an area of cutaneous thickening with a pebbled surface that on biopsy is a **connective tissue nevus**. The term *shagreen* derives from a type of leather that is embossed by knobs during the course of processing.

193. Which types of facial port wine stains are most strongly associated with ophthalmic or CNS complications?

Port wine stains can occur as isolated cutaneous birthmarks or, particularly in the areas underlying the birthmark, in association with structural abnormalities in the following areas: (1) the choroidal vessels of the eye, thereby leading to glaucoma; (2) the leptomeningeal vessels of the brain, thus leading to seizures (Sturge-Weber syndrome); and (3) hemangiomas in the spinal cord (Cobb syndrome). Glaucoma or seizures are most often associated with port wine stains in children demonstrating the following:

- Involvement of the eyelids
- Bilateral distribution of the birthmark
- Unilateral involvement of all three branches (V_1, V_2, V_3) of the trigeminal nerve
- Ophthalmologic assessment and radiologic studies (CT or MRI) are commonly used for screening, but there is no evidence that presymptomatic diagnosis of Sturge-Weber syndrome results in better neurodevelopmental outcomes.

Zallmann M, Leventer RJ, Mackay MT, et al. Screening for Sturge-Weber syndrome: a state-of-the art review. *Pediatr Dermatol.* 2018;35(1):30–42.

Tallman B, Tan OT, Morelli JG, et al. Location of port wine stains and the likelihood of ophthalmic and/or central nervous system complications. *Pediatrics.* 1991;87(3):323–327.

194. What are the three stages of incontinentia pigmenti?

Incontinentia pigmenti is an X-linked dominant disorder that is associated with seizures and mental retardation. Ectodermal tissues, such as eyes, nails, hair, and teeth, are also affected. The condition is presumed to be lethal to boys in utero because nearly 100% of cases are female. There are rare cases of XY patients with incontinentia pigmenti. It is caused by mutations in the *NEMO* (**N**F-kappaB **e**ssential **mo**dulator) gene, which is involved in cellular signal transduction.

- **Stage 1—*Vesicular stage*:** Lines of blisters are present on the trunk and extremities of the newborn that disappear in weeks or months. They may resemble herpetic vesicles. Microscopic examination of the vesicular fluid demonstrates eosinophils.
- **Stage 2—*Verrucous stage*:** Lesions develop in the patient at about 3 to 7 months of age that are brown and hyperkeratotic, resembling warts; these disappear over 1 to 2 years.

- **Stage 3—*Pigmented stage*:** Whorled, swirling (marble cake–like), macular, hyperpigmented lines develop. These may fade over time, leaving only remnant hypopigmentation in late adolescence or adulthood (which is sometimes considered a fourth stage).

195. What is the likely diagnosis for a 7-year-old who is noted to have recurrent nosebleeds, cutaneous telangiectasias on his lips, and an intracranial arteriovenous malformation on MRI?

This child has **hereditary hemorrhagic telangiectasia**, which has also been known as *Osler-Weber-Rendu disease.* This condition may affect up to 1 in 5000 children in the United States. The condition consists of nosebleeds; skin, lip, and oral mucosal lesions (Fig. 13.7); visceral manifestations due to arteriovenous malformations in the lung, liver, gastrointestinal tract, and CNS; and a positive family history. Genetic mutations involve transforming growth factor-β, which causes abnormalities in blood vessel formation.

Giordano P, Lenato GM, Lastella P, et al. Hereditary hemorrhagic telangiectasia: arteriovenous malformations in children. *J Pediatr.* 2013;163(1):179–183.

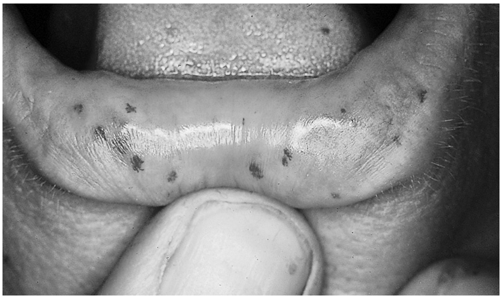

Fig. 13.7 Hereditary hemorrhagic telangiectasia with lip telangiectasia. (From Habif TP, ed. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 5th ed. Philadelphia, PA: Elsevier; 2011:911.)

NEUROMUSCULAR DISORDERS

196. How can the anatomic site responsible for muscle weakness be determined clinically?

See Table 13.9.

Table 13.9 Clinical Determination of Anatomic Site Responsible for Muscle Weakness

	UPPER MOTOR NEURON	ANTERIOR HORN CELL	NEUROMUSCULAR JUNCTION	PERIPHERAL NERVE	MUSCLE
Tone	Increased (may be decreased acutely)	Decreased	Normal, variable	Decreased	Decreased
Distribution	Pattern (e.g., hemiparesis, paraparesis) Distal > proximal	Variable, asymmetric	Fluctuating, cranial nerve involvement	Nerve distribution	Proximal > distal
Reflexes	Increased (may be decreased early)	Decreased to absent	Normal (unless severely involved)	Decreased to absent	Decreased
Babinski	Extensor	Flexor	Flexor	Flexor	Flexor
Other	Cognitive dysfunction, atrophy only very late	Fasciculations, atrophy, no sensory involvement	Fluctuating course	Sensory nerve involvement, atrophy, rare fasciculations	No sensory deficits; may be tenderness and signs of inflammation

Adapted from Packer RJ, Berman PH. Neurologic emergencies. In Fleisher GR, Ludwig S, eds. *Textbook of Pediatric Emergency Medicine.* 3rd ed. Baltimore, MD: Williams & Wilkins; 1993:584.

197. What are the causes of acute generalized weakness?

- **Infectious and postinfectious conditions:** Acute infectious myositis, GBS, enteroviral infection
- **Metabolic disorders:** Acute intermittent porphyria, hereditary tyrosinemia
- **Neuromuscular blockade:** Botulism, tick paralysis
- **Periodic paralysis:** Familial (hyperkalemic, hypokalemic, normokalemic)

Fenichel GM. *Clinical Pediatric Neurology: Signs and Symptoms Approach*. 5th ed. Philadelphia, PA: Elsevier; 2009:197.

198. If a child presents with weakness, what aspects of the history and physical examination suggest a myopathic process?

History

- Gradual rather than sudden onset
- Proximal weakness (e.g., climbing stairs, running) rather than distal weakness (more characteristic of neuropathy) predominates
- Absence of sensory abnormalities, such as “pins-and-needles” sensations
- No bowel and bladder abnormalities

Physical examination

- Proximal weakness is greater than distal weakness (except in myotonic dystrophy)
- Positive Gowers sign (see question 199)
- Neck flexion weaker than neck extension
- During the early stages, reflexes normal or only slightly decreased
- Normal sensory examination
- Muscle wasting but no fasciculations
- Muscle hypertrophy seen in some dystrophies

Weiner HL, Urion DK, Levitt LP. *Pediatric Neurology for the House Officer*. Baltimore, MD: Williams & Wilkins; 1988:136–138.

199. What is the significance of a Gowers sign?

Weakness of truncal and **proximal lower extremity muscles**. Most classically seen in Duchenne muscular dystrophy, the sign describes the manner in which children turn prone to rise and then rise from a sitting position by grasping and pushing on the knees and thighs (“climbing up the thighs”) until they are standing (Fig. 13.8). The adaptation of a prone position before rising is an important early feature because only 6.5% of healthy children still roll prone before standing. After age 3 years, any child with a need to turn prone before rising should be followed closely for a possible underlying neuromuscular condition.

Wallace GB, Newton RW. Gowers’ sign revisited. *Arch Dis Child.* 1989:64(9):1317–1319.

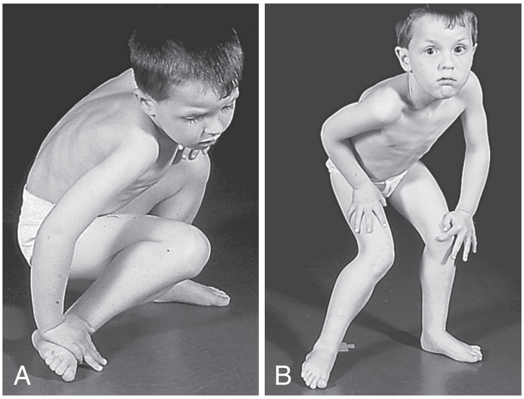

Fig. 13.8 Gowers sign. (A) A child turns prone to rise and begins to use his hands to push his body upright, (B) finally pushing off his knees/thighs before standing. (From Lissauer T, Clayden G, Craft A. *Illustrated Textbook of Paediatrics*. 4th ed. London: Elsevier; 2012: 488.)

200. How does electromyography help differentiate between myopathic and neurogenic disorders?

Electromyography measures the electrical activity of resting and voluntary muscle activity. Normally, the action potentials are of standardized duration and amplitude, with two to four distinguishable phases. In *myopathic* conditions, the durations and amplitudes are shorter than expected, called *brief, small-amplitude potentials (BSAPs);* in *neuropathies,* they are longer. In both conditions, extra phases (i.e., polyphasic units) are usually noted.

201. How is pseudoparalysis distinguished from true neuromuscular disease?

Pseudoparalysis (hysterical paralysis) or weakness may be seen in conversion reactions (i.e., emotional conflicts presenting as symptoms). In conversion reactions, sensation, deep tendon reflexes, and Babinski response are normal; movement may also be noted during sleep. **Hoover sign** is also helpful in cases of unilateral paralysis. With the patient lying supine on the table, the examiner places a hand under the heel of the affected limb and asks the patient to raise the unaffected limb. In pseudoparalysis, the examiner will feel pressure on the hand as the patient involuntarily extends the weak hip.

202. Why is it important to localize the cause of hypotonia?

Localization of the level of the lesion is critical for determining the nature of the pathologic process. In the absence of an acute encephalopathy, the differential diagnosis of hypotonia is best approached by asking the question, “Does the patient have normal strength despite the hypotonia, or is the patient weak and hypotonic?” The combination of weakness and hypotonia usually points to an abnormality of the anterior horn cell or the peripheral neuromuscular apparatus, whereas hypotonia with normal strength is more characteristic of brain or spinal cord disturbances.

KEY POINTS: HYPOTONIA

1. Localization of lesion is critical for determining pathologic process.
2. Most important question: Is strength normal or abnormal?
3. Hypotonia *with weakness*: Think abnormality in anterior horn cell or peripheral neuromuscular apparatus.
4. Hypotonia *without weakness*: Think brain or spinal cord disturbance.

203. How can you detect myotonia clinically?

Myotonia is a painless tonic spasm of muscle that follows voluntary contraction, involuntary failure of relaxation, or delayed muscle relaxation after a contraction. It can be elicited by grip (e.g., handshake), forced eyelid closure (or delayed eye opening in crying infants), lid lag after upward gaze, or percussion over various sites (e.g., thenar eminence, tongue).

204. How do the presentations of the two forms of myotonic dystrophy differ?

The presentation of **congenital** myotonic dystrophy is during the immediate newborn period. Symptoms include hypotonia; facial diplegia with “tenting” of the upper lip; and, frequently, severe respiratory distress as a result of intercostal and diaphragmatic weakness, especially in the right hemidiaphragm. Feeding problems as a result of poor suck and gastrointestinal dysmotility are also present. The **juvenile** presentation of this condition is during the first decade of life. This form is characterized by progressive weakness and atrophy of the facial and sternocleidomastoid muscles and shoulder girdle, impaired hearing and speech, and excessive daytime sleepiness. Clinical myotonia is more likely, and there may be mental retardation.

205. In a newborn with weakness and hypotonia, what obstetric and delivery features suggest a diagnosis of congenital myotonic dystrophy?

A history of spontaneous abortions, polyhydramnios, decreased fetal movements, delays in second-stage labor, retained placenta, and postpartum hemorrhage all raise the concern for *congenital myotonic dystrophy*. Because the mother is nearly always affected in congenital myotonic dystrophy (although previously diagnosed in only one-half of the cases), a careful clinical and electromyographic evaluation of the mother is essential. It is always important to shake the hand of the mother (barring religious exclusions), because affected women may not be able to release their hand after a handshake.

206. How is myotonic dystrophy an example of the phenomenon of “anticipation”?

Genetic studies have shown that the defect in myotonic dystrophy is an expansion of a trinucleotide (CTG) in a gene on the long arm of chromosome 19 that codes for a protein kinase. The gene product was named *myotonin-protein kinase,* and it is thought to be involved in sodium and chloride channel function. In successive generations, this repeating sequence tends to increase, sometimes into the thousands (normal is <40 CTG repeats), and the extent of repetition correlates with the severity of the disease. Thus, each succeeding generation is likely to get more extensive manifestations and earlier presentations of the disease (i.e., the phenomenon of “anticipation”). This trinucleotide repeat phenomenon is also seen in Huntington disease and fragile X syndrome.

207. How does the pathophysiology of infant botulism differ from that of foodborne and wound botulism?

- *Infant botulism* results from the ingestion of *Clostridium botulinum* spores that germinate, multiply, and produce toxin in the infant’s intestine. This is called a *toxi-infection.* The source of the spores is often unknown, but it has been linked to honey in some cases, and spores have been found in corn syrups. Therefore, these foods are not advised for infants younger than 1 year old.

- *Foodborne botulism* involves cases in which preformed toxin is already present in the food. Improper canning and anaerobic storage permit spore germination, growth, and toxin formation, which result in symptoms if the toxin is not destroyed by proper heating.
- *Wound botulism* occurs if spores enter a deep wound and germinate.

Rosow LK, Strober JB. Infant botulism: review and clinical update. *Pediatr Neurol.* 2015;52(5):487–492.

208. What is the earliest indication for intubation in an infant with botulism?

Intubation is indicated if there is a **loss of protective airway reflexes**. This occurs before respiratory compromise or failure because diaphragmatic function is not impaired until 90% to 95% of the synaptic receptors are occupied. An infant with hypercarbia or hypoxia is at very high risk for imminent respiratory failure.

Schreiner MS, Field E, Ruddy R. Infant botulism: a review of 12 years' experience at the Children's Hospital of Philadelphia. *Pediatrics.* 1991;87(2):159–165.

209. In an infant with severe weakness and suspected botulism, why is the use of aminoglycosides relatively contraindicated?

The botulism toxin acts by irreversibly blocking acetylcholine release from the presynaptic nerve terminals. Aminoglycosides, tetracyclines, clindamycin, and trimethoprim also interfere with acetylcholine release; therefore, they have the potential to act synergistically with the botulinum toxin to worsen or prolong neuromuscular paralysis.

210. What are the two most common symptoms in children with juvenile myasthenia gravis?

Ptosis and **diplopia**. Myasthenia gravis is characterized by a highly variable clinical course of fluctuating weakness (characteristically with increasing contractions) that initially involves muscles that are innervated by the cranial nerves. It is caused by a defect in neuromuscular transmission that is caused by an autoimmune antibody–mediated attack on the acetylcholine receptors.

211. What are the risks to a neonate who is born to a mother with myasthenia gravis?

Passively acquired neonatal myasthenia develops in about 10% of infants born to myasthenic mothers because of the transplacental transfer of antibody directed against acetylcholine receptors (AChRs) in striated muscle. Signs and symptoms of weakness typically arise within the first hours or days of life. Pathologic muscle fatigability commonly causes feeding difficulty, generalized weakness, hypotonia, and respiratory depression. Ptosis and impaired eye movements occur in only 15% of cases. The weakness virtually always resolves as the body burden of anti-AChR immunoglobulins diminishes. Symptoms typically persist for about 2 weeks but may require several months to disappear completely. General supportive treatment is usually adequate, but oral or intramuscular neostigmine may help diminish symptoms.

212. How does the pathophysiology of juvenile versus congenital myasthenia gravis differ?

Juvenile (and adult) myasthenia gravis is caused by circulating antibodies to the AChR of the postsynaptic neuromuscular junction. Occurrence is rare before the age of 2 years. *Congenital myasthenia gravis* is a nonimmunologic process. It is caused by morphologic or physiologic features affecting the presynaptic and postsynaptic junctions, including defects in ACh synthesis, end-plate acetylcholinesterase deficiency, and end-plate AChR deficiency. *Neonatal myasthenia gravis* refers to the transient weakness that occurs in infants of mothers with myasthenia gravis.

Peragallo JH. Pediatric myasthenia gravis. *Semin Pediatr Neurol.* 2017;24(2):116–121.

213. What was the edrophonium (Tensilon) test?

Edrophonium (brand name Tensilon) is a rapid-acting anticholinesterase that improves symptoms of myasthenia gravis by inhibiting the breakdown of ACh and increasing its concentration in the neuromuscular junction. Following IV administration, if measurable improvement in ocular muscle or extremity strength occurred, a diagnosis of myasthenia gravis was more likely. However, the test had the potential of significant side effects (e.g., cholinergic crisis) and high rates of false-negative and false-positive results, and is now mainly an historical footnote. The drug is no longer available in the United States and other countries.

214. Does a negative antibody test exclude the diagnosis of juvenile myasthenia gravis?

No. Up to 90% of children with juvenile myasthenia have measurable anti-AChR antibodies, but in the other 10%, continued clinical suspicion is necessary because their symptoms are usually milder (e.g., ocular muscle weakness, minimal generalized weakness). In these children, other tests (e.g., electrophysiologic studies, single-fiber electromyography) may be needed to make the diagnosis.

Della Marina A, Trippe H, Lutz S, Schara U. Juvenile myasthenia gravis: recommendations for diagnostic approaches and treatment. *Neuropediatrics.* 2014;45(2):75–83.

215. What are the four characteristic features of damage to the anterior horn cells?

Weakness, **fasciculations**, **atrophy**, and **hyporeflexia**.

216. What processes can damage the anterior horn cells?

- **Degenerative** (spinal muscular atrophy): Werdnig-Hoffmann, Kugelberg-Welander
- **Metabolic:** Tay-Sachs disease (hexosaminidase deficiency), Pompe disease, Batten disease (ceroid-lipofuscinosis), hyperglycinemia, neonatal adrenoleukodystrophy
- **Infectious:** Poliovirus, coxsackie virus, echoviruses

217. What is the primary genetic abnormality in infants and children with spinal muscular atrophy (SMA)?

Disruption of the **survival motor neuron 1 *(SMN1)* gene**. SMAs are a group of diseases that affect the motor neuron, resulting in widespread muscular denervation and atrophy. Incidence is estimated at 1 in 6000 to 10,000 newborns with a carrier frequency between 1 in 40 and 1 and 60. SMAs are the second most common hereditary neuromuscular disease after Duchenne muscular dystrophy. Extra copies of the *SMN2* gene (a companion protein-coding gene) modify the clinical outcome. It is uncertain how changes in the SMN protein result in the disease process, and it is unclear what causes the phenotypic variability. In 2019, the FDA approved gene therapy (Zolgensma), which delivers a fully functional copy of human *SMN* gene via an adeno-associated virus vector into target motor neuron cells, as treatment for children <2 years of age with SMA.

Bharucha-Goebel D, Kaufmann P. Treatment advances in spinal muscular atrophy. *Curr Neurol Neurosci Rep.* 2017;17(11):91.
Spinal Muscular Atrophy Association. www.smafoundation.org. Accessed January 22, 2020.

218. How are the inherited progressive SMAs distinguished?

See Table 13.10.

Table 13.10 Progressive Spinal Muscular Atrophies (SMAs)

DISORDER	INHERITANCE	AGE OF ONSET	CLINICAL FEATURES
Acute infantile SMA (Werdnig-Hoffmann disease, SMA type 1)	Autosomal recessive	In utero to 6 mo	Frog-leg posture; areflexia; tongue atrophy and fasciculations, progressive swallowing, and respiratory problems; survival <4 yr
Intermediate SMA (chronic Werdnig-Hoffmann disease, SMA type 2)	Autosomal recessive; rarely autosomal dominant	3 mo to 15 yr	Proximal weakness; most sit unsupported; decreased or absent reflexes; high incidence of scoliosis, contractures; survival may be up to 30 yr
Kugelberg-Welander disease (SMA type 3)	Autosomal recessive; rarely autosomal dominant	5-15 yr	May be part of the spectrum of SMA 2; hip girdle weakness; calf hypertrophy; decreased or absent reflexes; may be ambulatory until fourth decade
Adult-onset SMA (SMA type 4)	Autosomal recessive	After age 30 years	Mild to moderate muscle weakness, most commonly proximal; tremors, twitching; normal life

Adapted from Parke JT. Disorders of the anterior horn cell. In McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB, eds. *Oski's Pediatrics: Principles and Practice.* 3rd ed. Philadelphia, PA: J.B. Lippincott; 1999:1959.

219. What are muscular dystrophies?

A *muscular dystrophy* is an inheritable myopathy that affects limbs or facial muscles and is progressive, with pathologic evidence of degeneration or regeneration without any abnormal storage material.

Muscular Dystrophy Association. www.mda.org. Accessed January 22, 2020.

220. What is the clinical importance of dystrophin?

Dystrophin is a muscle protein that is presumed to be involved in anchoring the contractile apparatus of striated and cardiac muscle to the cell membrane. As a result of a genetic mutation, this protein is completely missing in patients with Duchenne muscular dystrophy. On the other hand, muscle tissue from patients with Becker muscular dystrophy contains reduced amounts of dystrophin or, occasionally, a protein of abnormal size.

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221. How are Duchenne and Becker muscular dystrophies distinguished?

See Table 13.11.

Table 13.11 Duchenne Versus Becker Muscular Dystrophy

	GENETICS	DIAGNOSIS	MANIFESTATIONS
Duchenne	1 in 3500 male births X-linked Several different deletions, point mutations in dystrophin gene result in a completely nonfunctional protein New mutations occur Carrier females may have mild weakness or cardiomyopathy	Whole-blood DNA may reveal a deletion in about 65%; otherwise, electromyogram and muscle biopsy studies are definitive	Clinically evident at 3-5 yr of age Regular, stereotyped course of progressive proximal weakness Calf hypertrophy Loss of ambulation by 9-12 yr Worsening scoliosis and contractures Eventual dilated cardiomyopathy and/or respiratory failure Life expectancy of 16-19 yr
Becker	1 in 20,000 male births X-linked Various mutations in dystrophin gene result in reduced amount of or partially functional protein	More benign clinical course Reduced dystrophin levels in muscle cells (by immunostaining) or abnormal dystrophin	Clinically evident during early second decade Milder, slower course compared with Duchenne Calf pseudohypertrophy Pes cavus Cardiac and central nervous system involvement unusual Ambulatory until 18 yr or beyond Life expectancy twice as long as compared with Duchenne

Adapted from Tsao VY, Mendell JR. The childhood muscular dystrophies: making order out of chaos. *Semin Neurol.* 1999:19:9-23.

222. What causes the calf hypertrophy seen in Duchenne muscular dystrophy?

Calf hypertrophy (Fig. 13.9) occurs primarily from replacement of muscle fibers with fat and fibrous tissue. When palpated, the calf has an unusually firm, rubbery feel. Other muscles, including the tongue, can be enlarged with replacement tissues.

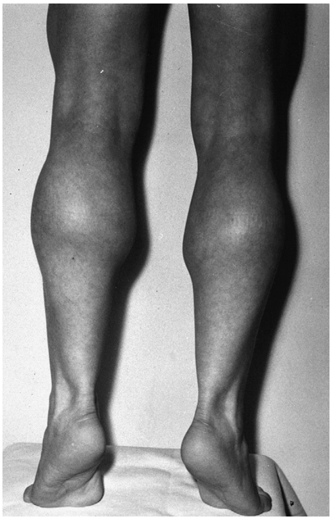

Fig. 13.9 Calf enlargement in Duchenne muscular dystrophy. (From Perkin GD, Miller DC, Lane R, et al, eds. *Atlas of Clinical Neurology.* 3rd ed. Philadelphia, PA: Saunders Elsevier; 2011:58.)

223. Is corticosteroid therapy effective for the treatment of Duchenne muscular dystrophy?

Several studies have documented an improvement in strength with an optimal dose of prednisone of 0.75 mg/kg per day. The strengthening effect lasts for up to 3 years while the steroid is continued. Despite medication and supportive care, loss of ambulation, respiratory failure, and compromised cardiac function remain the inevitable outcomes. However, clinical trials are currently underway using gene therapy, which could eventually revolutionize the treatment of the disease.

Chamberlain JR, Chamberlain JS. Progress toward gene therapy for Duchenne muscular dystrophy. *Mol Ther.* 2017;25(5):1125–1131.

224. What is the most likely diagnosis in a child with progressive walking difficulties evolving over several days?

GBS is an acute demyelinating neuropathy that is characterized by ascending, acute, progressive peripheral and cranial nerve dysfunction and paresthesias. In younger children (<6 years), it may be heralded by pain. It is frequently preceded by a viral respiratory or gastrointestinal illness. The disease is characterized by the presence of multifocal areas of the inflammatory demyelination of nerve roots and peripheral nerves. As a result of the loss of the healthy myelin covering, the conduction of nerve impulses (action potentials) may be blocked or dispersed. Axonal injury may also occur. The resulting clinical effects are predominantly motor (i.e., the evolution of flaccid, areflexic paralysis). There is a variable degree of motor weakness. Some individuals have mild brief weakness, whereas fulminant paralysis occurs in others. Autonomic signs (e.g., tachycardia, hypertension) and sensory symptoms (e.g., painful dysesthesias) are not uncommon, but they are overshadowed by the motor signs. More than half of these patients develop facial involvement, and mechanical ventilation may be required.

Ryan MM. Pediatric Guillain-Barré syndrome. *Curr Opin Pediatr.* 2013;25(6):689–693.
Yuki N, Hartung H-P. Guillain-Barré syndrome. *N Engl J Med.* 2012;366(24):2294–2304.

225. What are subtypes of GBS?

Subtypes are classified based on the clinical picture, laboratory results (including antiglycoside autoantibody patterns) and results of electromyography (EMG) and nerve conduction velocity (NCV) studies, which differentiate the relative effect of damage from either demyelination or axonal injury. One commonly used classification is:

- **AIDP: A**cute **i**nflammatory **d**emyelinating **p**olyneuropathy. This is the primary demyelinating form. EMG/NCV studies show evidence of demyelination of both motor and sensory nerves. In North America and Europe, 90% of cases of GBS involve this type.
- **AMSAN: A**cute **m**otor-**s**ensory **a**xonal **n**europathy. The axon of the nerve is considered to be the primary target, with secondary loss of myelin.
- **AMAN: A**cute **m**otor **a**xonal **n**europathy. Motor nerves alone are affected without sensory loss. EMG does not show demyelination. Axonal variants (AMSAN and AMAN) are much more frequent in Asia, accounting for 40% to 50% of cases.
- **Variants:** *Miller Fisher syndrome (MFS)* is characterized by gait ataxia, areflexia, and ophthalmoparesis. *Bickerstaff encephalitis* is brainstem encephalitis with encephalopathy in addition to the features seen in MFS. Both are associated with autoantibodies to glycoside GQ1b.

Arcila-Londono X, Lewis RA. Guillain-Barré syndrome. *Semin Neurol.* 2012;32(3):179–186.

226. What CSF findings are characteristic of GBS?

The classic CSF finding is the **albuminocytologic dissociation**. Most common infections or inflammatory processes generate an elevation of WBC count and protein. The CSF profile in GBS includes a normal cell count with elevated protein, usually in the range of 50 to 100 mg/dL; however, at the onset of disease, the CSF protein concentration may be normal.

227. How are children with acute GBS managed?

Early clinical monitoring is focused on the development of bulbar or respiratory insufficiency. Bulbar weakness manifests as unilateral or bilateral facial weakness, diplopia, hoarseness, drooling, depressed gag reflex, or dysphagia. Frank respiratory insufficiency may be preceded by air hunger, dyspnea, or a soft muffled voice (hypophonia). The autonomic nervous system is occasionally involved, and this is signified by the presence of cardiac arrhythmia, labile blood pressure and body temperature, and urinary retention. The management of GBS includes the following:

- Observation in an intensive care unit is critical, with frequent monitoring of vital signs.
- The early institution of IVIG or plasmapheresis shortens the clinical course and lessens long-term morbidity; corticosteroid therapy is thought to be ineffective.
- If bulbar signs are present, the patient should receive nothing orally, and the mouth must be suctioned frequently. Hydration is maintained intravenously, and nutritional support is provided by nasogastric feedings.

- The vital capacity (VC) is measured frequently. In children, the normal VC may be calculated as VC = 200 mL × age in years. If the VC falls below 25% of normal, endotracheal intubation is performed. Careful pulmonary toilet is conducted to minimize atelectasis, aspiration, and pneumonia.
- Meticulous nursing care includes careful patient positioning to prevent pressure sores, compression of peripheral nerves, and venous thrombosis.
- Physical therapy is conducted to prevent the development of contractures by passive range-of-movement exercises and splinting to maintain physiologic hand and limb postures until muscle strength returns.

Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet.* 2016;13;388(10045):717–727.

Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev.* 2014;9: CD002063.

Agrawal S, Peake D, Whitehouse WP. Management of children with Guillain-Barré syndrome. *Arch Dis Child Educ Pract Ed.* 2007;92(6):161–168.

228. What is the prognosis for children with GBS?

Children appear to recover more quickly and more fully than adults. Most have good neurologic recovery, although approximately 20% to 40% may have some longer-term residual symptoms (including paresthesias and fatigue). In children, the long-term outcome is not substantially different among the GBS subtypes. In rare cases, the neuropathy may recur as a chronic inflammatory demyelinating polyneuropathy (CIDP). There is debate whether CIDP is a long-term continuation of AIDP or a separate illness with a different pathogenesis.

Roodbol J, de Wit MC, Aarsen FK, et al. Long-term outcome of Guillain-Barré in children. *J Peripher Nerv Syst.* 2014;19(12):121–126.

Vajsar J, Fehlings D, Stephens D. Long-term outcome in children with Guillain-Barré syndrome. *J Pediatr.* 2003;142(3):305–309.

GGS/CIDP Foundation International. www.gbs-cidp.org. Accessed January 10, 2020.

229. Does multiple sclerosis present during childhood?

Uncommonly. It is estimated that about 3% to 5% of patients with multiple sclerosis experience their first attack <18 years of age, and onset <10 years is quite uncommon (<1%). Studies of affected children demonstrate a variable predominance of boys during early childhood and females during adolescence. Ataxia, muscle weakness, and transient visual or sensory symptoms are relatively common presentations. CSF examination may demonstrate mild (<25 cells/mm^3) mononuclear pleocytosis with an increasing probability of oligoclonal bands with each recurrence. MRI is the single most useful diagnostic test: the presence of multiple periventricular white matter plaques (bright areas on T2 images) confirms the diagnosis.

Bigi S, Banwell B. Pediatric multiple sclerosis. *J Child Neurol.* 2012;27(11):1378–1383.

SPINAL CORD DISORDERS

230. Which sacral dimples and coccygeal pits in a newborn are concerning for an occult spinal dysraphism (OSD)?

These occur in up to 4% of newborns. Isolated simple sacral dimples are rarely associated with a significant spinal abnormality. However, certain features are more likely to be associated with an OSD (such as tethered cord syndrome) and warrant a screening ultrasound.

- Location above the gluteal crease (typically >2.5 cm from the anus)
- Deep dimples (if base cannot be visualized, do not probe because of risk for introducing an infection if a direct communication with the spinal canal is present)
- Larger size (>0.5 cm)
- Pits with cutaneous markers (lipoma, hypertrichosis, hemangioma)

Kucera JN, Coley I, O'Hara S, et al. The simple sacral dimple: diagnostic yield of ultrasound in neonates. *Pediatr Radiol.* 2015;45(2):211–216.

Williams H. Spinal sinuses, dimples, pits and patches: what lies beneath? *Arch Dis Child Educ Pract Ed.* 2006;91:75–80.

KEY POINTS: NEONATAL SACRAL FINDINGS SUGGESTIVE OF OCCULT SPINAL DYSRAPHISM

1. Location above the gluteal crease (typically >2.5 cm from the anus)
2. Deep dimples
3. Larger dimple size (>0.5 cm)
4. Sacral pits with cutaneous markers (lipoma, hypertrichosis, hemangioma)

231. What are the two main features of Chiari malformations?

Cerebellar elongation and **protrusion of the foramen magnum into the cervical spinal cord**. Anatomic anomalies of the hindbrain and skeletal structure result in different positioning of the various structures relative to the upper cervical canal and foramen magnum with different clinical features.

232. What are the types of Chiari malformations?

- **Type I** is the most common but clinically the least severe, and is generally asymptomatic during childhood. It is often diagnosed as an incidental finding on cervical MRI scans for neck pain and/or headache. The presentation of a Chiari I malformation may be insidious. There may be paroxysmal vertigo, drop attacks, vague dizziness, and headache, which may be increased by the Valsalva maneuver. Occipital headache precipitated by exertion may progress to torticollis, down-gaze nystagmus, periodic nystagmus, and oscillopsia (objects in the visual field oscillate). MRI findings include malformations of the base of the skull and of the upper cervical spine, including hydromyelia and syringomyelia, which is a cyst (or syrinx) in the spinal cord that can expand and elongate over time. Surgical treatment is typically reserved only for symptomatic patients or those with a syrinx.
- **Type II** is the so-called "classic" Chiari malformation (known historically as *Arnold-Chiari malformation*). Medulla and cerebellum, together with part or the entire fourth ventricle, are displaced into the spinal canal (Fig. 13.10). A variety of cerebellar, brainstem, and cortical defects can occur. This type is strongly associated with noncommunicating hydrocephalus and lumbosacral myelomeningocele.
- **Type III** comprises any of the features of types I and II, but the entire cerebellum is herniated throughout the foramen magnum, with a cervical spina bifida cystica. Hydrocephalus is a common feature.

Baisden J. Controversies in Chiari I malformations. *Surg Neurol Int.* 2012;3(Suppl 3):S232–S237.

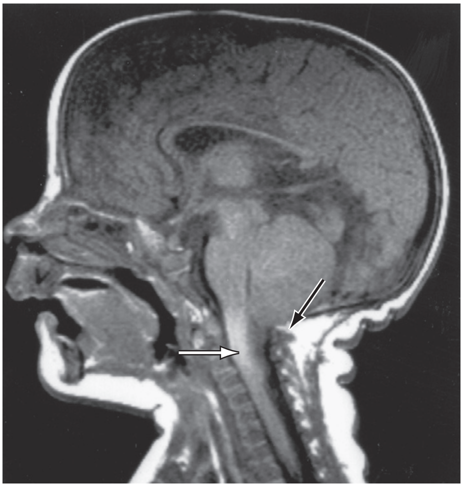

Fig. 13.10 A midsagittal T1-weighted MRI of a patient with type II Chiari malformation. The cerebellar tonsils *(white arrow)* have descended below the foramen magnum *(black arrow).* Note the small, slit-like fourth ventricle, which has been pulled into a vertical position. (From Kleigman RM, Stanton BF, Schor NF, et al, eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:2009.)

KEY POINTS: EARLY CLUES TO SPINAL CORD COMPRESSION

1. Scoliosis producing sustained poor posture
2. Back or abdominal pain beginning abruptly during sleep
3. Increased sensitivity of spinal column to local pressure or percussion
4. Bowel or bladder dysfunction
5. Diminished sensation in the anogenital region and lower limbs

233. What are the types of spina bifida?

Spina bifida refers to malformations that result from failure of the neural tube to close at the caudal end, as well as the overlying vertebral arches, during embryogenesis. This can range from an asymptomatic defect, such as spina bifida occulta in which the two halves of the vertebral arch fail to close, to increasing displacement of the spinal cord (myelomeningocele), to the most severe form, myeloschisis, with exposed nervous tissue surrounded by no membrane (Fig. 13.11).

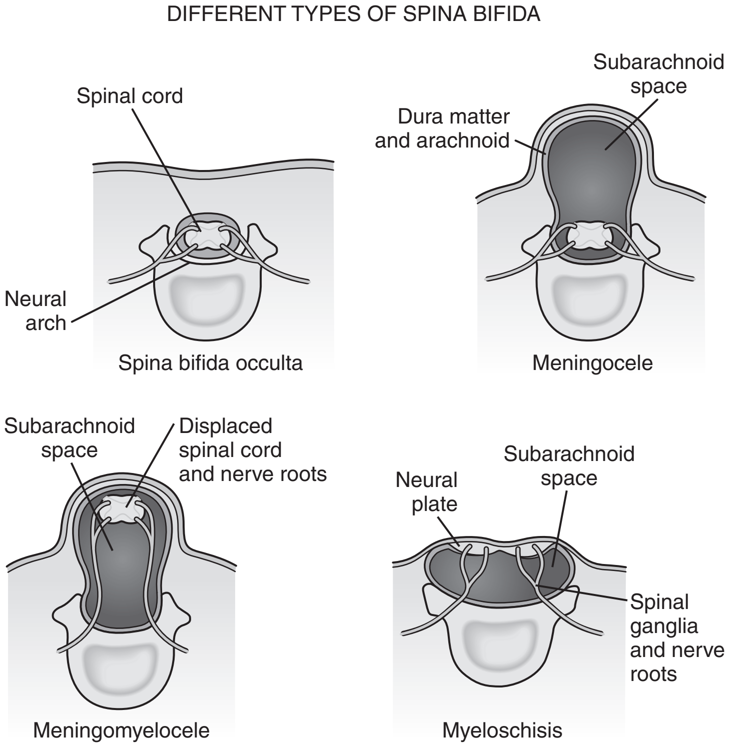
DIFFERENT TYPES OF SPINA BIFIDA
Spinal cord
Neural arch
Spina bifida occulta
Subarachnoid space
Dura matter and arachnoid
Meningocele
Subarachnoid space
Displaced spinal cord and nerve roots
Meningomyelocele
Neural plate
Subarachnoid space
Spinal ganglia and nerve roots
Myeloschisis

Fig. 13.11 The different types of spinal bifida. (From Perkin GD, Miller DC, Lane R, et al, eds. *Atlas of Clinical Neurology*. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2011:267.)

234. How common are asymptomatic spinal anomalies in normal children?

Up to 5% of children have *spina bifida occulta,* an incomplete fusion of the posterior vertebral arches, which is usually noted as an incidental radiographic finding. The defect most commonly involves the lower lumbar lamina of L5 and S1.

235. What is the full anatomic expression of myelomeningocele?

- The presence of unfused or excessively separated vertebral arches of the bony spine (spina bifida)
- Cystic dilation of the meninges that surround the spinal cord (meningocele)
- Cystic dilation of the spinal cord itself (myelocele)
- Hydrocephalus and the spectrum of congenital cerebral abnormalities

236. What is the likelihood that a patient with myelomeningocele will have hydrocephalus?

Hydrocephalus is seen in 95% of children with thoracic or high lumbar myelomeningocele. The incidence decreases progressively with more caudal spinal defects to a minimum of 60% if the myelomeningocele is located in the sacrum.

237. What is the usual cause of stridor in a child with myelomeningocele?

The stridor is usually caused by **dysfunction of the vagus nerve**, which innervates the muscles of the vocal cords. In their resting position, the edges of the cords meet in the midline; during speech, they move apart. Hence, in bilateral palsies of the vagus nerve, the free edges of the vocal cords are closely opposed and obstruct air flow, thereby resulting in stridor. In symptomatic patients, the motor nucleus of the vagus nerve may be congenitally hypoplastic or aplastic. More commonly, the vagal dysfunction is believed to arise from a mechanical traction injury caused by hydrocephalus, which produces progressive herniation and inferior displacement of the abnormal hindbrain. Shunting the hydrocephalus may alleviate the traction and improve the stridor. Sometimes the later recurrence of stridor indicates the reaccumulation of hydrocephalus as a result of ventriculoperitoneal shunt failure.

238. What are the principal options for managing urinary incontinence in patients with myelomeningocele?

About 80% of patients have a neurogenic bladder, which most commonly manifests as a small, poorly compliant bladder and an open and fixed sphincter. Options include the following:

- Clean intermittent catheterization, which results in more complete emptying than simple Credé maneuvers
- Artificial urinary sphincter to increase outlet resistance
- Surgical urinary diversion (e.g., suprapubic vesicostomy), which is uncommonly used
- Augmentation cystoplasty to increase bladder capacity in combination with the use of oxybutynin (a smooth muscle antispasmodic)

Mourtzinos A, Stoffel JT. Management goals for the spina bifida neurogenic bladder: a review from infancy to adulthood. *Urol Clin North Am.* 2010;37(4):527–535.

239. How frequently is myelomeningocele associated with intellectual disability?

Only 15% to 20% of patients have associated intellectual disability (mental retardation). Hydrocephalus *per se* does not cause the mental retardation that is associated with this syndrome. Children with appropriately treated congenital hydrocephalus caused by simple aqueductal stenosis usually have normal psychomotor development. Only severe hydrocephalus with a very thick cortical mantle predicts lower intelligence. Intellectual disability is usually attributed to acquired secondary CNS infection or subtle microscopic anomalies of neuronal migration and differentiation, which may coexist with the macroscopically visible malformation of the hindbrain.

240. In an infant born with myelomeningocele, how does the initial evaluation predict long-term ambulation potential?

The level of motor function—and not the level of the defect—is most predictive of ambulation.

- **Thoracic:** No hip flexion is noted. Almost no younger children will ambulate, and only about one-third of adolescents will ambulate with the aid of extensive braces and crutches.
- **High lumbar (L1, L2):** The patient is able to flex the hips, but there is no knee extension. About one-third of children and adolescents will ambulate, but only with extensive assistive devices.
- **Mid-lumbar (L3):** The patient is able to flex the hips and extend the knee. The percentage of those able to ambulate is midway between those with high and low lumbar lesions.
- **Low lumbar (L4, L5):** The patient is able to flex the knee and dorsiflex the ankle. Nearly half of younger children and nearly all adolescents will ambulate, with varying degrees of braces or crutches.
- **Sacral (S1–S4):** The patient is able to plantar flex the ankles and move the toes. Nearly all children and adolescents will ambulate with minimal or no assistive devices.

241. How can neural tube defects be prevented?

All women of reproductive age should receive 400 micrograms of folic acid each day, in addition to consuming food with folate from a varied diet, to help prevent neural tube defects. Folic acid supplementation should begin at least 1 month before conception. In women with a history of having a child with a neural tube defect, higher doses of folate (4 milligrams) are recommended.

Viswanathan M, Treiman KE, Doto JK, et al. Folic acid supplementation for the prevention of neural tube defects: an updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;317(2):190–203.

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ONCOLOGY

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CHAPTER 14

CHEMOTHERAPY AND RADIATION THERAPY

1. What are the most common cytotoxic chemotherapeutic drug classes, and in which cell cycle phase are they the most active?

Chemotherapeutic drugs are usually classified by their primary site and mechanism of action or source. The most common ones are the **alkylators, antimetabolites, antitumor antibiotics**, and **plant toxins**. See Fig. 14.1.

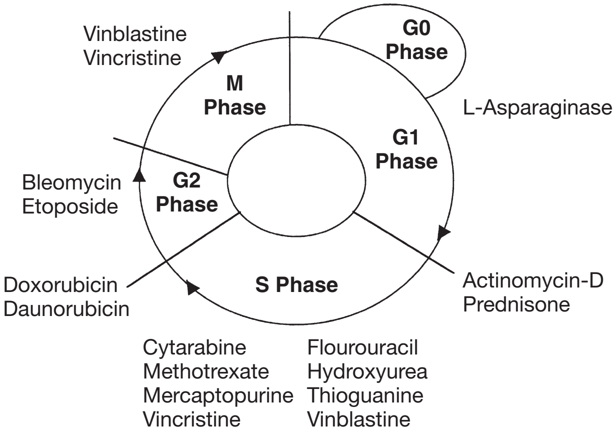

Fig. 14.1 Phases in which cell cycle–dependent chemotherapy agents are most active. *G0,* resting phase (nonproliferation); *G1,* gap1 (pre-DNA synthesis with diploid RNA and protein synthesis); *S,* DNA synthesis; *G2,* gap2 (post-DNA synthesis); *M,* mitosis. (From Weiner MA, Cairo MS. *Pediatric Hematology/Oncology Secrets.* Philadelphia, PA: Hanley & Belfus; 2000:96.)

2. What is the difference between adjuvant and neoadjuvant chemotherapy?

- *Adjuvant chemotherapy* is administered *after* the primary treatment of a tumor (surgical resection or radiation therapy), when there is no remaining gross tumor that can be assessed for response to the chemotherapy.
- *Neoadjuvant chemotherapy* is administered *before* the delivery of definitive local treatment and then continues afterward in the adjuvant setting. For children with solid tumors, several cycles of neoadjuvant chemotherapy are often administered to improve the chances of achieving complete surgical resection and improved local control of a primary tumor.

3. Why are most chemotherapeutic drug dosages based on body surface area (BSA)?

In theory, *BSA* correlates better than body weight with cardiac output and hence hepatic and renal perfusion. Because most drug clearance occurs by hepatic and renal mechanisms, anticancer drugs that have a very narrow therapeutic index are usually dosed in a manner that is normalized to BSA. The exception is made for infants, who have a very high BSA–to–body weight ratio; these infants receive chemotherapy based on body weight.

BSA can be estimated using height and weight. It can be obtained with the following formula:

$$\text{BSA}\left(\text{m}^2\right) = \sqrt{[(\text{Weight} \times \text{height})/3600]}$$

4. What is the difference between pharmacokinetics and pharmacodynamics?

- *Pharmacokinetics* refers to the effect of the body on the drug. It is the study of how drugs are absorbed, distributed, metabolized, and eliminated from the body. Common parameters include elimination half-life, peak concentration, clearance, and area under the concentration-time curve.
- *Pharmacodynamics* refers to the effect of the drug on the body. A pharmacodynamic effect can be a toxicity measurement (decrease in blood counts) or an anticancer measurement (decrease in the size of a tumor) after chemotherapy.

5. What are the phases of clinical trials?

- **Phase I:** *The dose determination phase*. This phase is designed primarily to recommend a dose for further testing in children, usually the maximum tolerated dose. Pharmacokinetic studies are performed during phase I trials to help learn whether children handle a drug differently than adults. Phase I trials typically enroll 9 to 30 children.
- **Phase II:** *The efficacy phase*. Usually a group of children with the same diagnosis is studied and the percentage of patients in whom the drug causes a tumor to decrease in size is determined. Phase II trials enroll 30 to 150 children, depending on how many different tumor types are being studied.
- **Phase III:** *The comparative phase*. This phase studies whether a new drug (or a new combination of drugs) that was found to be efficacious in a phase II trial can improve therapy relative to the best current therapy. Phase III trials are randomized and can enroll hundreds to thousands of children.
- **Phase IV:** *The postmarketing surveillance phase.* This phase occurs after a product has been approved by the Food and Drug Administration (FDA) and examines real-world experiences. Phase IV trials examine the long-term safety and potential side effects of a product, cost-effectiveness, and comparative analysis with other drugs. Phase IV trials can involve thousands of children.

Balis FM, Fox E, Widemann BC, Adamson PC. Clinical drug development for childhood cancers. *Clin Pharmacol Ther.* 2009;85(2):127–129.

6. Why is intrathecal chemotherapy dose based on patient age, whereas systemic (oral, intravenous [IV]) dosing is based on weight or BSA?

The brains of children grow disproportionately more quickly than their bodies. The cerebrospinal fluid (CSF) increases in parallel with central nervous system (CNS) growth, such that by the age of 3 years, CSF volume is 80% that of adult CSF volume. Scaling intrathecal doses to body size would undertreat younger children, whereas scaling doses in adolescent patients, whose CNS size has plateaued relative to body size, would unnecessarily expose them to potentially more toxic drug concentrations.

7. What antiemetic agents are most effective in the management of chemotherapy-induced nausea and vomiting?

The **serotonin receptor antagonists** (ondansetron, granisetron, and palonosetron) act as the foundation of prophylactic therapy for chemotherapy with significant emetogenic potential. The **neurokinin (NK1) receptor antagonists** (e.g., aprepitant) are the newest class of effective antiemetic agents and have shown extremely promising results. Aprepitant blocks the NK1 receptors in the vomiting centers in the CNS, which are activated by substance P, released as an unwanted consequence of chemotherapy. **Benzodiazepines** and **first-generation H1-receptor antagonists** (diphenhydramine, hydroxyzine) are also widely used due to their potent antiemetic and anxiolytic effects. **Corticosteroids** are useful for chemotherapeutic agents with low emetic potential; however, they are most effective when used in combination with other agents. Less effective agents include **metoclopramide**, **cannabinoids**, and **olanzapine**, all of which have a greater potential for adverse side effects.

Phillips RS, Friend AJ, Gibson F, et al. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. *Cochrane Database Syst Rev.* 2016;2:CD007786.

Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med.* 2008;358(23):2482–2494.

8. What is the major dose-limiting toxicity for the alkylating agents?

Myelosuppression. Alkylating agents are chemically reactive compounds that covalently add an alkyl group; this is most important with regard to macromolecules involved in DNA synthesis, damaging templates, and inhibiting synthesis. Agents include the nitrogen mustards, (e.g., cyclophosphamide, ifosfamide, melphalan), nitrosoureas (carmustine, streptozocin), and alkyl sulfonates (busulfan). Platinum drugs, including carboplatin and cisplatin, act in a similar manner. They permanently coordinate to DNA to interfere with DNA repair, so they are described as “alkylating-like.”

9. What is the best way to minimize possible myelosuppression?

Many chemotherapy agents significantly affect the bone marrow, resulting in myelosuppression, which can manifest in anemia, thrombocytopenia with increased risk for bleeding, and severe neutropenia (absolute neutrophil count <500). Neutropenia, especially when lasting for several weeks, can place the patient at risk for bacterial and fungal infections and can also delay the subsequent cycles of chemotherapy. Filgrastim (Neupogen), a granulocyte colony–stimulating factor, can be administered after the completion of the chemotherapy cycle to reduce the amount of time a patient stays in a neutropenic phase. It stimulates the bone marrow to produce granulocytes and release them into the circulation.

Dale DC, Crawford J, Klippel Z, et al. A systematic literature review of the efficacy, effectiveness, and safety of filgrastim. *Support Care Cancer.* 2018;26(1):7–20.

10. If one had to choose a single laboratory test to obtain before administering high-dose methotrexate, which one should it be?

Determination of serum creatinine is essential before administering high-dose methotrexate. The kidneys eliminate more than 90% of methotrexate. In the presence of abnormal renal function, high-dose methotrexate carries a high risk for severe or fatal toxicity. To increase methotrexate solubility and excretion, the urine has to be alkalinized (pH 7 or greater) with IV fluid containing sodium bicarbonate.

Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist.* 2006;11(6):694–703.

11. What factors are associated with an increased risk for developing anthracycline-induced cardiotoxicity?

Total cumulative dose, mediastinal radiotherapy, young age, and **female gender** are associated with an increased risk for developing anthracycline (doxorubicin, daunorubicin)-induced cardiotoxicity. Cumulative anthracycline dose has long been associated with an increased risk, with the incidence of clinically apparent congestive heart failure rising significantly with doxorubicin doses exceeding 450 mg/m^2. Late cardiotoxicity appears to be more common in children than in adults because the heart is unable to grow in proportion to the child, resulting in a small, poorly compliant left ventricle. Thus younger children, particularly children younger than 5 years, are at higher risk. There is also some evidence that girls have a higher incidence of abnormal cardiac findings at any given cumulative dose than boys. Trisomy 21 and black patients may also be at increased risk. Dexrazoxane, a cardioprotective agent, has been used in adults receiving anthracyclines, but the FDA has limited pediatric use because of possible higher rates of second malignancies and acute myelogenous leukemia (AML) in patients treated for different cancers.

Bansal N, Amdani S, Lipshultz ER, Lipshultz SE. Chemotherapy-induced cardiotoxicity in children. *Expert Opin Drug Metab Toxicol.* 2017;13(8):817–832.

Barry E, Alvarez JA, Scully RE, et al. Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. *Expert Opin Pharmacother.* 2007;8(8):1039–1058.

12. How did a periwinkle plant contribute to some long-standing chemotherapeutic agents?

Extractions from the pink Madagascar periwinkle plant have been used for centuries as natural remedies. When used (unsuccessfully) as a treatment for diabetes mellitus, myelosuppression was noted. In the 1950s, the active components were noted to be **vinca alkaloids**. This property led to studies in oncology, with vincristine (one of the alkaloids) licensed by the FDA in 1963. Vincristine binds to tubulin, which disrupts microtubules and arrests mitosis in metaphase; thus it is most effective in rapidly dividing cell types. Vincristine continues to play a role in the treatment of a variety of pediatric cancers. Common complications, however, include constipation, alopecia, and peripheral neuropathy with loss of deep tendon reflexes.

Liesveld J, Asselin B. It's ALL in the liposomes: vincristine gets a new package. *J Clin Oncol.* 2013;31(6):657–659.

Moudi M, Go R, Yien CY, et al. Vinca alkaloids. *Int J Prev Med.* 2011;11(4):1231–1235.

13. We can thank the guinea pig for a major (albeit serendipitous) breakthrough in the treatment of childhood acute lymphoblastic leukemia (ALL). What was the role played by our friend of the Caviidae rodent family?

In 1953, investigators discovered that whole guinea pig serum could bring about regression of certain transplanted lymphosarcomas in inbred mice. By 1961, it was determined that the fraction of guinea pig serum responsible for its antileukemic effect contained significant **asparaginase** activity. Most leukemic lymphoblasts were then found to be asparagine autotrophs, requiring exogenous asparagine for survival. A bacterial source *(Escherichia coli)* of asparaginase was identified, and pharmaceutical production of L-asparaginase began, increasing the complete remission rate for children with ALL from about 80% to more than 95%. Its most common side effect is allergic reaction. It is given in the form of PEG-asparaginase, with PEG standing for polyethylene glycol. By conjugating the native enzyme to this large polymer, the half-life of the drug is greatly extended and the exposed antigenic sites that can result in allergic reactions are diminished.

14. A 10-year-old girl is being treated for AML with a combination of high-dose cytarabine and daunorubicin. Five days after the initiation of therapy, she develops the onset of nystagmus, ataxia, and dysmetria; however, computed tomography (CT) of the brain reveals no focal abnormalities. What is the most likely cause of her symptoms?

High-dose cytarabine can result in an **acute cerebellar syndrome** leading to nystagmus, ataxia, dysmetria (lack of coordination of movement), and dysdiadochokinesia (impaired ability to perform rapidly alternating movements). Imaging at the onset of symptoms is typically normal. In most cases, neurologic symptoms resolve within a week, but as many as 30% of patients do not regain full cerebellar function. The risk for developing cerebellar syndrome is related to the dose and schedule of cytarabine, with the highest risk being observed with administration of high doses over 6 or more days. Other side effects of cytarabine include fever, rash, and conjunctivitis, which can be prevented with dexamethasone eye drops.

15. What are the most common side effects of steroids?

Steroids (prednisone and dexamethasone) are one of the backbones of therapy for ALL, but the beneficial effects come with a price. The most common side effects include increased appetite, central obesity, hypertension, hyperglycemia, osteoporosis, poor wound healing, acne, cataracts, psychological problems, myopathy, and increased risk for infections. Sudden withdrawal after long-term treatment with corticosteroids can lead to adrenal insufficiency.

16. What are the long-term sequelae of chemotherapy?

Today, approximately 80% of children with cancer are cured. However, significant long-term effects from chemotherapy have come to the forefront with a growing population of survivors. The effects are based on the type of treatment received and the age at which the patient was treated. The major sequelae include **cognitive defects**, **cardiac defects** (particularly with anthracyclines), **endocrinopathies** (especially thyroid dysfunction and hypopituitarism), **infertility**, and, unfortunately, **secondary malignancies**. There is a significant component of **psychosocial morbidity**, including depression and anxiety, which has been reported.

Skinner R. Long-term effects of cancer therapy in children—functional effects, late mortality and long-term follow-up. *Paediatr Child Health.* 2012;22:248–252.

Skinner R. Long-term effects of cancer therapy in children—organs, systems and tissues. *Paediatr Child Health.* 2012;22:201–206.

17. Which classes of chemotherapeutic agents have most commonly been implicated in causing secondary leukemias?

Secondary leukemia is a collective term used to describe a group of patients with AML or myelodysplastic syndrome (MDS) who have a history of environmental, occupational, or therapeutic exposure to hematotoxins or radiation. The **alkylating agents** (e.g., cyclophosphamide) and **topoisomerase II inhibitors** (etoposide) are the most important drugs, which increase the risk for developing secondary leukemia. Etoposide-induced leukemias tend to occur earlier, usually within 2 to 3 years of exposure. Most commonly the cells harbor cytogenetic abnormalities in chromosomes 5 and 7.

18. What are the differences between conventional external radiation, intensity-modulated radiation therapy (IMRT), and proton-beam radiation?

Both *conventional radiation* and *IMRT* use photon or electron beams to deliver radiation to the patient. IMRT uses many radiation fields, with each field having a unique radiation intensity profile that varies as a function of position within the field. This differs from conventional radiation, in which each field has a constant, or fixed, intensity profile across the field area and thus allows for dose reduction to normal tissues or critical structures. Because of the physical properties of protons and their ability to deposit energy over a short distance, *proton therapy* may have the advantage of reducing radiation dose to nontarget normal tissue while allowing higher doses to be delivered to the tumor.

19. Who develops the "somnolence syndrome"?

Transient symptoms attributed to temporary demyelination have been observed 6 to 8 weeks after **completion of CNS radiation**, most commonly for CNS prophylaxis for ALL. Children who develop the somnolence syndrome have lethargy, headache, and anorexia that last for about 2 weeks. CT and CSF studies show no consistent abnormality, but an electroencephalogram often reveals a slow-wave activity consistent with diffuse cerebral disturbance. The use of steroids during irradiation appears to minimize the occurrence of the syndrome.

20. What is radiation recall?

Radiation recall is a delayed effect that results from the interaction of certain chemotherapeutic agents (doxorubicin, daunorubicin, or actinomycin-D) with radiation. After radiation therapy, an erythematous rash in the previous radiation field develops. The rash is geographic, usually precisely following the outline of the radiation field. Many of these occur months after the radiation treatment.

21. What are the long-term effects of radiation therapy?

Radiation therapy is an important component of treatment for many pediatric cancers. However, it is associated with the development of **secondary neoplasms** (solid tumors), **obesity** after cranial radiation, **thyroid dysfunction**, and **pulmonary** and **cardiac** complications. The majority of these complications arise within the field of exposure. Limiting the dose and the extent of radiation exposure is key in reducing the long-term effects.

Armstrong GT, Stovall M, Robison LL. Long-term effects of radiation exposure among adult survivors of childhood cancer: results from the Childhood Cancer Survivor Study. *Radiation Res.* 2010;174(6):840–850.

22. How does immunotherapy work?

Cancer immunotherapy of various types attempts to stimulate a patient's immune system to destroy tumors. *Monoclonal antibodies* specifically target certain antigens (such as rituximab, which is an anti-CD20 antibody). *Cellular therapies* stimulate a patient's white blood cells outside of the body to recognize and eliminate cancer cells when returned to the patient. *Chimeric antigen receptor T cells* (CAR-T cells), which target CD19-positive cells, are the latest FDA-approved immunotherapy for pediatric ALL. Tumors express a number of protein antigens that can be recognized by T cells and thus provide potential targets for immunotherapy. Dendritic cells have the potential to present antigens to T cells. Dendritic cells incubated with tumor antigens and administered as a cellular vaccine were found to have therapeutic effects against different tumor types. Tumors can use inhibitory immune checkpoints to protect themselves from the attacks of the immune system. *Immune checkpoint inhibitors* can unleash the immune response against the tumor. One example of a checkpoint inhibitor is the PD-1 inhibitor pembrolizumab.

Wedekind MF, Denton NL, Chen CY, Cripe TP. Pediatric cancer immunotherapy: opportunities and challenges. *Paediatr Drugs.* 2018;20(5):395–408.

23. What is targeted therapy?

Targeted therapy is a form of molecular medicine. The drug interferes with specific targeted molecules, which are part of a signal transduction pathway essential in the growth or survival of the cancer cells. These agents are expected to be more effective and less harmful to normal cells than the conventional chemotherapy. One of the most successful targeted therapies is the tyrosine-kinase inhibitor imatinib, which targets the oncofusion protein Bcr-Abl, the main driver of chronic myeloid leukemia. Also, the BRAF inhibitor vemurafenib is used to treat melanoma and certain brain tumors harboring *BRAF* V600E mutation.

Smith MA, Reaman GH. Remaining challenges in childhood cancer and newer targeted therapies. *Pediatr Clin North Am.* 2015;62(1):301–312.

24. What does personalized medicine mean?

Personalized medicine, also called *precision medicine,* uses information about the genes, proteins, and environment of a patient's tumor to treat it in the most efficient way. The tumor's genes are compared with the patient's genes to give information not only about the cancer but also how the patient's unique molecular and genetic profile might increase susceptibility to certain diseases in the future. Based on these genetic results, the medical treatment is tailored to the individual characteristic of the cancer. Personalized medicine can also be helpful in determining the effectiveness of a treatment and favorability of prognosis.

Forrest SJ, Geoerger B, Janeway KA. Precision medicine in pediatric oncology. *Curr Opin Pediatr.* 2018;30(1):17–24.

CLINICAL ISSUES

25. A patient has a central venous catheter and develops a fever. What should be done?

The risk for bacteremia is increased in patients with central venous catheters. As such, any patient with an indwelling central venous catheter and a fever (temperature usually $\geq$101.3°F [38.5°C]) should have paired blood cultures drawn from the catheter (one or more catheter lumens) and from a peripheral vein before any antibiotic administration. IV antibiotics are typically administered until evidence of a negative blood culture is provided. Removal of the catheter should be considered if the patient has signs of sepsis, significant worsening erythema, or purulence. Removal of the catheter is generally advised if blood cultures are positive with a suspected pathologic organism. If the catheter is left in place, it should be removed if bloodstream infection continues despite $>$72 hours of antimicrobial therapy to which the infecting microbes are susceptible. If catheter removal is required, the catheter tip should be cultured.

Mermel LA, Allon M, Bouza, et al. Clinical practice guidelines for diagnosis and management of intravascular catheter-related infection, 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49(1):1–45.

Rackoff WR, Ge J, Sather HN, et al. Central venous catheter use and the risk of infection with acute lymphoblastic leukemia: a report from the Children's Cancer Group. *J Pediatr Hematol Oncol.* 1999;21(4):260–267.

26. Which bacteria do patients with AML have an increased susceptibility to? What antibiotic coverage do they require?

Streptococci viridans. Gram-positive coverage with **vancomycin** is typically added.

27. A patient undergoing chemotherapy is neutropenic and has a fever. What should be done?

Because neutropenic patients are at risk for invasive bacterial infections, patients who are neutropenic (absolute neutrophil count $<500/\text{mm}^3$ or $<1000/\text{mm}^3$ and falling) should have blood cultures obtained and receive broad-spectrum antibiotics. Antibiotic coverage should include both gram-negative and gram-positive organisms, including antibiotics that are active against *Pseudomonas aeruginosa*. Broad-spectrum antibiotics are continued until blood cultures have been negative for 48 hours, a patient has been afebrile for at least 24 hours, and there is marrow evidence (with increasing neutrophil counts) that indicate signs of recovery.

Lehrnbecher T. Treatment of fever in neutropenia in pediatric oncology patients. *Curr Opin Pediatr.* 2019;31(1):35–40.

Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol.* 2017;35(18):2082–2094.

28. A patient remains febrile and neutropenic despite appropriate antibiotics for several days. Is there cause for concern?

Although it is not uncommon for a neutropenic patient to remain febrile for many days despite administration of broad-spectrum antibacterial agents, persistent fever is associated with an **increased likelihood of invasive fungal infection**. Pediatric patients at particular risk for invasive fungal disease are those with AML or relapsed acute leukemia, those receiving highly myelosuppressive chemotherapy for other malignancies, and those undergoing stem cell transplantation with fever $\geq$96 hours despite broad-spectrum antibiotic therapy and with neutropenia that is expected to continue $>$10 days. Because the ability to recover fungi in routine blood cultures is limited, the approach to such patients is to empirically add antifungal coverage after a period of persistent fever. Choices of empirical antifungal therapy have expanded over recent years and now include liposomal formulations of amphotericin B, azoles (e.g., voriconazole), and echinocandins (e.g., caspofungin).

Lehrnbecher T. Treatment of fever in neutropenia in pediatric oncology patients. *Curr Opin Pediatr.* 2019;31(1):35–40.
Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol.* 2017;35(18):2082–2094.

29. After receiving broad-spectrum antibiotic therapy for 4 days for fever and neutropenia, a patient develops a new fever that is associated with abdominal cramps and bloody diarrhea. What is the most likely diagnosis?

The patient most likely has ***Clostridioides (formerly Clostridium) difficile* colitis** brought on by treatment with broad-spectrum antibiotics. The diagnosis should be confirmed by detection of the *C. difficile* toxins in the stool, and either metronidazole (preferred) or oral vancomycin should be initiated promptly.

30. A 10-year-old in her second year of treatment for ALL has had all medications voluntarily stopped by her parents for 8 weeks. What is the likely diagnosis when she presents to the emergency department with cough, tachypnea, hypoxia, and a chest x-ray that reveals widespread pulmonary infiltrates?

***Pneumocystis jiroveci* pneumonia (PJP).** Formerly called *pneumocystis carinii, P. jiroveci* are yeastlike fungi that can result in opportunistic infections in individuals with compromised immune systems. Although classified as a fungus, PJP is nonresponsive to antifungal treatment. Children with cancer are immunosuppressed both because of their underlying diagnosis and the chemotherapy they receive. As a result, they require PJP prophylaxis (typically trimethoprim-sulfamethoxazole), which is given as 2 to 3 consecutive days of dosing per week. In this case, a compliance failure likely resulted in pneumonia. Clinical signs of *Pneumocystis* pneumonia can be highly variable, but a classic feature is an arterial oxygen level (Pao_2) that is distinctly lower than expected given the clinical findings.

31. What paraneoplastic syndromes can occur in childhood?

Paraneoplastic signs or symptoms are those that are unrelated to a malignancy but that can herald cancer. They occur more commonly in adults than in children. However, unexplained high calcium, watery diarrhea, polymyositis, dermatomyositis, unexplained high hemoglobins, hypertension, precocious puberty, encephalitis, and opsoclonus or myoclonus can be associated with childhood malignancies.

Wells EM, Dalmau J. Paraneoplastic neurologic disorders in children. *Curr Neurol Neurosci Rep.* 2011;11(2):187–194.

32. What is hyperleukocytosis, and how is it treated?

Hyperleukocytosis is defined as a peripheral leukocyte count $>$100,000/mL. It can cause CNS hemorrhage, thrombosis, pulmonary leukostasis, and metabolic derangements. Treatment is with IV hydration, allopurinol, or rasburicase. Coagulation abnormalities should be corrected, and patients who are symptomatic may require exchange transfusion and/or leukapheresis. Clinically significant hyperleukocytosis is seen with AML and CML.

33. What are the metabolic abnormalities in tumor lysis syndrome?

Tumor lysis syndrome is an oncologic emergency that occurs when there is spontaneous or chemotherapy-induced massive breakdown of tumor cells. The subsequent release of the cells' contents into the circulation leads to **hyperkalemia**, **hyperuricemia**, **hyperphosphatemia**, and **secondary hypocalcemia**. Hyperkalemia is the most dangerous aspect of tumor lysis syndrome because of the high risk for sudden death. As such, patients at risk for tumor lysis syndrome should have no potassium placed in their IV fluids, have frequent electrolyte checks, and may need to be placed on a cardiac monitor.

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med.* 2011;364(19):1844–1854.

34. What are the current recommendations regarding management of tumor lysis syndrome?

Prevention is the key in the management of tumor lysis syndrome and is done through **aggressive IV hydration**. The goal of IV hydration is to quickly improve renal perfusion and glomerular filtration, which results in high urine output that minimizes the likelihood of uric acid or calcium phosphate precipitation in the tubules. There is no current consensus regarding the role of urinary alkalization by using sodium bicarbonate in these patients. Reducing the level of uric acid through pharmacologic measures is also recommended.

35. What two pharmacologic agents can be used to prevent or treat hyperuricemia caused by tumor lysis syndrome?

Allopurinol inhibits the enzyme xanthine oxidase, a key enzyme required for the formation of uric acid. Its administration blocks further uric acid *production*. **Rasburicase** is a recombinant enzyme that catalyzes the conversion of uric acid to allantoin, which is more soluble than uric acid and more readily *excreted* by the kidney.

36. What type of malignancy is associated with rapid tumor lysis and abdominal distention?

Burkitt lymphoma. It is important to note that the risk for worsening tumor lysis increases upon initiation of treatment, and some patients require continuous venovenous hemofiltration (CVVH) to support them through this event.

37. A child with newly diagnosed leukemia experiences a rapid decline in hemoglobin soon after administration of rasburicase. What is the basis for this drug-related adverse event?

Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency because of the risk for hemolysis and development of methemoglobinemia.

38. A child undergoing induction chemotherapy for leukemia develops right lower quadrant pain and tenderness. What diagnosis should be considered?

Typhlitis. Although patients with cancer or those receiving chemotherapy may develop appendicitis, typhlitis is a severe necrotizing infection of the ileocolonic junction that occurs in neutropenic patients.

39. What is the difference between a Broviac and a Port-A-Cath?

Children who require repeated blood draws or IV medications often have a semi-permanent central venous catheter placed.

- A *Broviac catheter* is tunneled through the subcutaneous tissues of the chest and emerges as a thin plastic tube, usually at the level of the second or third rib.
- A *Port-A-Cath* contains a subcutaneous reservoir and is implanted under the skin of the chest. It is not visible, but it must be accessed by inserting a small needle through the skin and into the reservoir.

Gallieni M, Pittiruti M, Biffi R. Vascular access in oncology patients. *CA Cancer J Clin.* 2008;58(6):323–346.

40. What is the differential diagnosis of an anterior mediastinal mass?

The five "Ts" can be used to remember the differential diagnosis of an anterior mediastinal mass: **t**eratoma (germ cell tumor), **t**hymoma, **t**hyroid tumor, **T**-cell leukemia, and **t**errible lymphoma (Fig. 14.2).

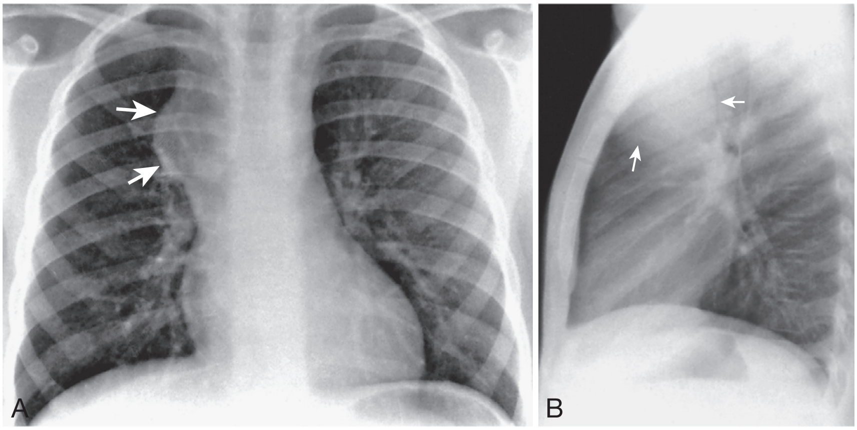

Fig. 14.2 (A) Frontal radiograph in a child with "leukemia/lymphoma" syndrome, demonstrating an anterior mediastinal mass *(arrows).* (B) Lateral film illustrates the anterior nature of the mass *(arrows)* with posterior displacement of the trachea. (From Blickman JG, Parker BR, Barnes PD. *Pediatric Radiology: The Requisites.* 3rd ed. Philadelphia, PA: Mosby; 2009:42.)

41. What is superior mediastinal syndrome? How is it managed?

Superior mediastinal syndrome, also called *superior vena cava syndrome,* results from the presence of an anterior mediastinal mass that compresses the trachea and the superior vena cava. Patients have a cough and dyspnea, particularly when supine, and they have swelling of the head and upper extremities as a result of venous compression. Patients with a large mediastinal mass must not be anesthetized because of the risk for complete airway obstruction and vascular collapse. The optimal management of a mediastinal mass is prompt diagnosis and the initiation of appropriate treatment. Irradiation of the mass may provide emergent relief while the diagnosis is being made.

42. What type of pleural effusion is seen with malignancy?

Exudative. Exudative effusions may be caused by malignancy or infection and typically result from inflammation. They are characterized by high cell counts and increased protein concentrations. This contrasts with transudative effusions, more typically seen in congestive heart failure or nephrotic syndrome, which have low cell counts and low protein content.

43. A patient who is receiving treatment for AML has persistent fever for 8 days and then acutely decompensates with hypotension and develops cytopenias, transaminitis, and coagulopathy. What diagnosis must be considered?

Hemophagocytic lymphohistiocytosis (HLH). This is a disorder of excessive immune activation with marked inflammation and tissue destruction involving multiple organs. Genetic abnormalities are commonly found. There is a familial form. Triggers of HLH can include viruses (e.g., Epstein-Barr virus [EBV], HIV), malignancies (most commonly lymphoid cancers and leukemia), and rheumatologic disorders (e.g., systemic juvenile idiopathic arthritis [JIA]). Per the HLH-2004 trial, diagnostic criteria include either a molecular diagnosis consistent with HLH (i.e., evidence of pathologic mutations) or five of the following eight criteria: fever $\geq$100.9°F (38.3°C), splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, biopsy-confirmed hemophagocytosis (in bone marrow [Fig. 14.3], spleen, lymph nodes, or liver), low or absent natural killer (NK) cell activity, elevated ferritin, or elevated soluble interleukin-2 (IL-2) receptor alpha (CD25).

Lehmberg K, Nichols KE, Henter JI, et al. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. *Haematologica.* 2015;100(8):997–1004.

Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48(2):124–131.

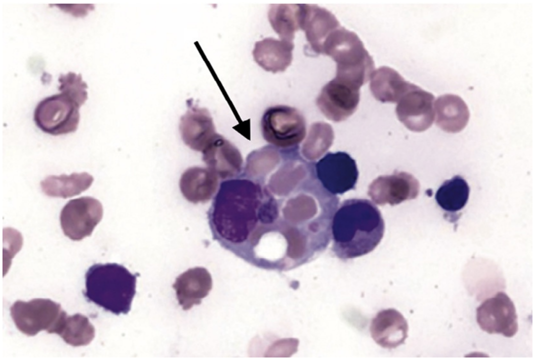

Fig. 14.3 EBV-associated hemophagocytic lymphohistiocytosis. Bone marrow aspirate shows phagocytosis of red blood cells *(arrow).* (From Jaffe ES, Arber DA, Campo E, et al, eds. *Hematopathology.* 2nd ed. Philadelphia, PA: Elsevier; 2007:568.)

44. Which neoplasms are associated with hemihyperplasia?

Wilms tumor, hepatoblastoma, adrenal cortical carcinoma, and **leiomyosarcomas** are associated with *hemihyperplasia* (formerly called *hemihypertrophy*) either as part of a syndrome (such as Beckwith-Wiedemann syndrome) or in isolation. Hemihyperplasia is due to abnormal proliferation of cells rather than an increase in size of existing cells (hemihypertrophy). It results in one side or portion of the body being larger than the other. The difference can be subtle (noted only when a patient lies on a flat surface) or more obvious when posture or gait is observed. Between 1% and 3% of Wilms tumor patients have hemihyperplasia.

45. Which cancers are often associated with splenomegaly?

Acute leukemia, **chronic myeloid leukemia**, **chronic myelomonocytic leukemia**, **Hodgkin disease**, and **non-Hodgkin lymphoma (NHL)** are often associated with splenomegaly. Solid tumors rarely metastasize to the spleen to the point of causing splenomegaly.

46. What signs or symptoms are suggestive of malignancy in a pediatric patient with peripheral lymphadenopathy?

A common clinical problem is determining which patients with enlarged lymph nodes require biopsy for diagnosis. Risk for malignancy is increased with **increasing size** (>1 cm in the neonatal period, >2 cm and increasing in older children despite antibiotic therapy), **increasing number** of adenopathy sites, and concurrent **systemic symptoms** (i.e., prolonged fever, night sweats, weight loss). Supraclavicular location, abnormal chest radiograph, abnormal complete blood count (CBC), and fixed nodes are also predictive of malignancy.

King D, Ramachandra J, Yeomanson D. Lymphadenopathy in children: refer or reassurance? *Arch Dis Child Educ Pract Ed.* 2014;99:101–110.

Soldes OS, Younger JG, Hirschl RB. Predictors of malignancy in childhood peripheral lymphadenopathy. *J Pediatr Surg.* 1999;34:1447–1452.

47. What is the function of the Langerhans cells?

These are **antigen-presenting immune cells**, dendritic in appearance, that are found in all layers of the skin and mucosal surfaces and in lymph nodes. The ultrastructural hallmark of the cell is the *Birbeck granule,* a cytoplasmic organelle that is shaped like a tennis racquet (Fig. 14.4).

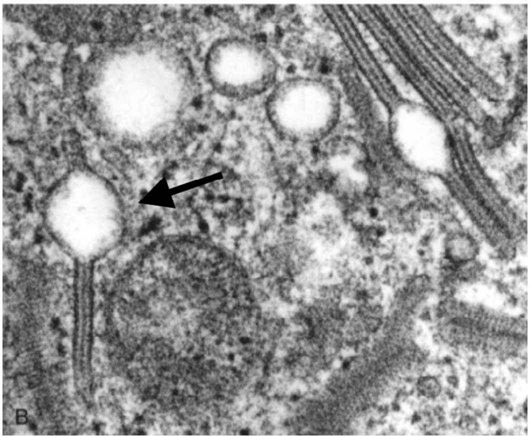

Fig. 14.4 Birbeck granule. Electron micrograph shows rodlike Birbeck granule, often with a dilated terminal end producing a tennis racquet–like appearance *(arrow).* (From Kumar V, Abbas AK, Aster JC, eds. *Robbins and Cotran Pathologic Basis of Disease.* 9th ed. Philadelphia, PA: Saunders/Elsevier; 2015:624.)

48. What are the features of Langerhans cell histiocytosis (LCH)?

LCH is a multifaceted disorder and replaces the diseases grouped under the term *histiocytosis X*. The presenting symptoms of LCH may be **isolated bone lesions** (*eosinophilic granuloma*), **bone lesions with exophthalmos and diabetes insipidus** (*Hand-Schüller-Christian disease*), or **bone lesions with disseminated disease** (*Letterer-Siwe disease*). Other features include skin rashes that resemble seborrheic dermatitis, chronic otitis externa, lymphadenopathy, hepatosplenomegaly, pancytopenia, neurologic deficits, and pulmonary disease. Mild forms of the disease tend to wax and wane even without treatment, whereas disseminated disease is often resistant to therapy.

Harmon CM, Brown N. Langerhans cell histiocytosis: a clinicopathologic review and molecular pathogenetic update. *Arch Pathol Lab Med.* 2015;139(10):1211–1214.

49. What is an eosinophilic granuloma?

Eosinophilic granuloma is a lytic tumor of bone that is accompanied by pain and sometimes swelling. Its histology is identical to that of LCH, with which it is now classified. Biopsy of an isolated eosinophilic granuloma is often curative, although lesions may also regress spontaneously.

50. What are the common indications for transfusion support for children with cancer?

Although there are no absolute criteria, in most centers, packed red blood cells are given when a patient has a hemoglobin level in the range of 6 to 8 g/dL, even if asymptomatic, or at higher levels if a patient has symptoms or if ongoing marrow suppression is anticipated. Platelets are empirically administered for a platelet count of <10,000 to 20,000/mm^3 in an otherwise well patient; a higher threshold may be used if there is active bleeding, disseminated intravascular coagulation (DIC), or a planned procedure. Granulocyte transfusions may be effective in neutropenic patients with a refractory infection caused by a gram-negative organism. Transfusions with plasma may be used for the treatment of coagulopathies.

Roseff SD, Luban NL, Manno CS. Guidelines fo ng appropriateness of pediatric transfusion. *Transfusion.* 2002;42(11):1398–1413.

51. What are the most common symptoms experienced by oncology patients receiving end-of-life care?

Fatigue, **pain**, and **dyspnea**. Parents report that these symptoms are managed effectively in less than one-third of children. Compared with adults, twice as many children die in hospitals (usually an intensive care unit [ICU]) during the final stages of disease, half on ventilators, and only 10% to 20% of dying children receive hospice care. This is despite the fact that 70% of families would choose for their child to die at home if support were adequate. Insufficient attention to palliative care has been a large problem, although an appreciation of its importance is growing.

Epelman CL. End-of-life management in pediatric cancer. *Curr Oncol Rep.* 2012;14:191–196.
Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. *N Engl J Med.* 2000;342:326–333.
National Hospice and Palliative Care Organization. www.nhpco.org/pediatrics. Accessed March 6, 2020.

EPIDEMIOLOGY

52. Although in psychic lore a "seer" can look into the future, SEER has a different connotation for cancer researchers. What is it?

SEER stands for the **S**urveillance, **E**pidemiology, and **E**nd-**R**esults database. SEER collects cancer incidence, prevalence, and survival data in specific geographic areas in the United States. These areas represent about 28% of the U.S. population. SEER data are freely available to qualified investigators and can be used to study epidemiologic trends in cancer incidence, prevalence, and survival.

National Cancer Institute. https://seer.cancer.gov Accessed March 6, 2020.

53. How do the types of cancers differ between adults and children?

As a general rule, in *adults,* most cancers are **carcinomas** (of epithelial origin). In *children,* the origin of most cancers are **reticuloendothelial** (e.g., leukemia, lymphoma), **embryonal** (e.g., blastomas), or **mesenchymal** (e.g., sarcomas). Childhood cancers are not strongly linked to lifestyle or environmental risk factors.

54. How do the types and frequency of childhood cancers vary by age?

See Table 14.1.

Table 14.1 Variation of Cancer Types and Frequency by Age

CHILDREN (AGES: 0-14 YR)	ADOLESCENTS (AGES: 15-19 YR)
Acute lymphoblastic leukemia: 26%	Hodgkin lymphoma: 15%
Brain and CNS tumors: 21%	Thyroid carcinoma: 11%
Neuroblastoma: 7%	Brain and CNS tumors: 10%
Non-Hodgkin lymphoma: 6%	Testicular germ cell tumors: 8%
Wilms tumor: 5%	Non-Hodgkin lymphoma: 8%
Acute myeloid leukemia: 5%	Acute lymphoblastic leukemia: 8%
Bone tumor: 4%	Bone tumors: 7%
Hodgkin lymphoma: 4%	Melanoma: 6%
Rhabdomyosarcoma: 3%	Acute myeloid leukemia: 4%
Retinoblastoma: 3%	Ovarian germ cell tumors: 2%

CNS, Central nervous system.
Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. *Ca Cancer J Clin.* 2014;64(2):83–103.

55. Where does cancer rank as a cause of death in children and young adults?

Although cancer is the leading cause of *disease-related* mortality in children 5 to 9 years of age, it is overall the second leading cause of death in this age group in the United States. It accounts for about 18% of deaths in children ages 5 to 9 years. In children ages 10 to 14 years, cancer is the third leading cause of death, accounting for 14% of deaths. Unintentional injuries, primarily motor vehicle accidents, and intentional self-harm are the two most frequent causes of death in children ages 5 to 14 years. Unintentional injuries are also the leading cause of death for adolescents and young adults, accounting for more than 38% of deaths. Homicides and suicides are responsible for almost 36% of deaths in this age group, with cancer being a distant fourth at 5.5%.

CDC, National Center for Health Statistics. Deaths, percent of total deaths, and death rates for the 15 leading causes of death in 5-year age groups, by race and Hispanic origin, and sex: Unite[illegible]tes, 2016. www.cdc.gov. Accessed February 12, 2019.

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56. What cancers are most commonly associated with a second neoplasm?

See Table 14.2.

Table 14.2 Cancers Most Commonly Associated With a Second Neoplasm

PRIMARY TUMORS	SECONDARY TUMORS
Retinoblastoma	Osteosarcoma Pineoblastoma
Hodgkin disease	Acute myeloid leukemia Non-Hodgkin lymphoma Thyroid carcinoma Sarcoma, breast cancer (in the radiation field)
Acute lymphoblastic leukemia	Brain tumors Non-Hodgkin lymphoma
Sarcoma	Other sarcomas

57. What are the most important cancer predisposition syndromes in children?

See Table 14.3.

Table 14.3 Cancer Predisposition Syndromes in Children

CANCER PREDISPOSITION SYNDROME	TYPE OF CANCER
Li-Fraumeni syndrome	Soft tissue sarcomas, osteosarcoma, breast cancer, brain tumors, leukemia, adrenocortical carcinoma
Neurofibromatosis type 1	Brain tumor, malignant peripheral nerve sheath tumor
Xeroderma pigmentosum	Skin cancer
DICER1 syndrome	Pleuropulmonary blastoma, thyroid cancer, Wilms tumor, ovarian tumor, embryonal rhabdomyosarcoma
Down syndrome	Leukemias, testicular tumor
Fanconi anemia	Myelodysplastic syndrome, acute myeloid leukemia, squamous cell carcinoma, hepatic tumors
Bloom syndrome	Leukemias, lymphomas, carcinomas (colon, breast, lung)

58. Which cancers have a significant racial predilection?

Wilms tumor has a higher incidence among black female infants. **Ewing sarcoma** is about 30 times more common in whites than in blacks. **Hodgkin disease** is rare in those of East Asian descent.

59. Are there any gender differences in childhood cancer?

More boys than girls are diagnosed with cancer. The gender effect in incidence of childhood cancer is well established: for all cancers, the boys-to-girls ratio is 1.2:1. There are a few exceptions, including carcinomas, malignant melanoma, infant leukemia, and soft tissue sarcoma. On the other hand, girls tend to have more severe treatment-related late effects; studies suggest associations between female sex and cognitive dysfunction after cranial irradiation, cardiovascular outcome, or obesity.

Armstrong GT, Sklar CA, Hudson MM, Robison LL. Long-term health status among survivors of childhood cancer: does sex matter? *J Clin Oncol.* 2007;25(28):4477–4489.

60. What are the most commonly used epidemiologic tools to study pediatric oncology?

- **Case-control study:** compares patients who have a disease (cases) with patients who do not have the disease (controls) and looks back to compare how frequently the risk factor is present in each group to determine the relationship between the risk factor and the disease
- **Cohort study**: one or more samples (called cohorts) are followed in time and subsequent evaluations with respect to a disease or outcome are conducted to determine which initial participants risk factors are associated with it
- **Randomized controlled trial**: randomly assigns participants into an experimental group or a control group and follows in time

- **Meta-analysis**: combines pertinent qualitative and quantitative study data from several selected studies to develop a single conclusion
- **Systematic analysis:** often written by a panel that provides a comprehensive review of all relevant studies on a particular clinical or health-related topic/question

61. What is bioinformatics?

Bioinformatics is an interdisciplinary field that develops methods and software to understand biologic data. It combines biology, computer science, and statistics. It helps analyze the mutations in cancer, gene, and protein expressions and to reveal interactions between signaling pathways.

62. Does cell phone usage increase the risk for cancers, specifically brain tumors?

Any connection between cell phones and cancer is controversial. Studies have been conflicting. Some suggest a relationship between long-term use ($>$10 years) of mobile and cordless phones and the development of certain CNS tumors, primarily gliomas and acoustic neuromas. However, the largest study to date, the INTERPHONE study involving 13 countries, found no increased risk. Cell phones emit radiofrequency electromagnetic fields (RF-EMFs), and obviously the brain is proximate during typical usage. In 2011, the International Agency for Research on Cancer (IARC) classified RF-EMFs as “possible” human carcinogens. Data are currently epidemiologic. Theories on the role of RF-EMF as potential initiators and promoters of stages of carcinogenesis at present remain speculative, but certainly do raise concern, given the high degree of cell phone usage and exposure in younger children and teenagers.

Yang M, Guo W, Yang C, et al. Mobile phone use and glioma risk: a systematic review and meta-analysis. *PLoS One.* 2017;12(5): e0175136.

INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol.* 2010;39:675–694.

63. Are there any known transplacental carcinogens?

Diethylstilbestrol, which was used to prevent spontaneous abortion, has been associated with an increased risk for vaginal cancer in female offspring. It has also been reported that there is a 10-fold increased risk for monoblastic leukemia in the infants of mothers who smoke **marijuana**. It has been suggested that sedatives and a number of nonhormonal drugs are transplacental carcinogens, but this has not been proven. It also has not been proven if cigarette smoke and the use of oral contraceptives are transplacental carcinogens.

64. Is the survival of pediatric cancer similar all around the world?

Unfortunately not. There are significant differences between developed countries (like the United States or Canada) and low-middle-income countries (parts of South America). Approximately 80% of the world’s children with cancer live in the developing world. Whereas the overall 5-year survival rate for most childhood cancers is around 80%, only 20% of patients are reported cured in low-income countries. Some reasons for this large gap are the lack of infrastructure and resources, cultural differences, inaccurate assessment of tumor burden, differences in incidence and characteristics of childhood cancer, and socioeconomic status and education. One solution to this problem is twinning partnerships between institutions in the developing countries and low-middle-income countries. Sharing knowledge and resources has been proven to create or expand capacity to treat pediatric cancer more successfully.

LEUKEMIA AND LYMPHOMA

65. What are the most common clinical findings in the initial presentation of ALL?

- **Hepatosplenomegaly:** 70% (10% to 15% of children have marked enlargement of the liver or spleen to a level below the umbilicus)
- **Fever:** 40% to 60%
- **Lymphadenopathy:** 25% to 50% with moderate or marked enlargement
- **Bleeding:** 25% to 50% with petechiae or purpura
- **Bone and joint pain:** 25% to 40%
- **Fatigue:** 30%
- **Anorexia:** 20% to 35%

KEY POINTS: ACUTE LYMPHOBLASTIC LEUKEMIA

1. Most common childhood malignancy
2. Increased risk: Patients with Down syndrome, congenital immunodeficiency syndrome, exposure to ionizing radiation, sibling of patient with ALL
3. Chemotherapy phases: Induction (to achieve remission), delayed intensification, maintenance
4. Survival (if in standard risk group) $>$80% at 5 years after completion of therapy
5. Most common sites of relapse: bone marrow, CNS, testis

66. What typical hematologic findings are noted during the presentation of ALL?

Leukocyte count (mm^3)

- $<$10,000: 45% to 55%
- 10,000 to 50,000: 30% to 35%
- $>$50,000: 20%

Hemoglobin (g/dL)

- $<$7.5: 45%
- 7.5 to 10.0: 30%
- $>$10: 25%

Platelet count (mm^3)

- $<$20,000: 25%
- 20,000 to 99,000: 50%
- $>$100,000: 25%

67. What studies of tumor cells are useful for determining a patient's prognosis?

- **Cytogenetics and ploidy (number of chromosomes):** Cytogenetics and DNA index (ratio of DNA content in abnormal cells compared with normal reference cells) are determinants of the number and structure of chromosomes and chromosomal material in tumor cells. More than 50 chromosomes or a DNA index of $>$1.16 is favorable, whereas $<$46 is a poor prognostic indicator. Certain chromosomal translocations are unfavorable.
- **Immunophenotyping** is also useful and involves the determination of B- or T-cell lineage, with maturity or immaturity of cells. Mature B-cell and precursor T-cell types have a poorer prognosis.

Harrison CJ. Cytogenetics of paediatric and adolescent acute lymphoblastic leukaemia. *Br J Haematol.* 2009;144(2):147–156.

68. Which patients with ALL have a poorer prognosis: younger or older children?

The prognosis for children diagnosed with **ALL $\le$12 months** has remained poor. Infant ALL appears to be a biologically distinct entity in comparison with ALL in older children, with infants generally having a conglomeration of adverse factors, including *MLL* (mixed gene leukemia) gene rearrangement (observed in up to 80% of infants with ALL), high presenting leukocyte counts, hepatosplenomegaly, CNS disease, and slow early response to therapy. The presence of MLL gene rearrangement (at chromosome 11, band q23) in infantile ALL requires increased intensification of chemotherapy.

Guest EM, Stam RW. Updates in the biology and therapy for infant acute lymphoblastic leukemia. *Curr Opin Pediatr.* 2017;29(1):20–26.
Chowdhury T, Brady HJ. Insights from clinical studies into the role of the MLL gene in infant and childhood leukemia. *Blood Cells Mol Dis.* 2008;40(2):192–199.
Silverman LB. Acute lymphoblastic leukemia in infancy. *Pediatr Blood Cancer.* 2007;49(7 Suppl):1070–1073.

69. Why do boys with ALL fare more poorly than girls?

In boys, after a full course of chemotherapy with remission, **testicular involvement** is a common site of relapse, occurring in up to 10% of cases. In older boys and teenage boys, there is a **higher incidence of T-cell disease** than in girls. T-cell disease is associated with adverse prognostic factors (high white blood cell count, hepatosplenomegaly, and mediastinal masses) and alone carries a poorer prognosis. In girls, ovarian relapse is very rare.

70. Are race and ethnicity related to treatment outcome in patients with acute leukemia?

Race and ethnicity appear to be related to outcome in ALL. Black, Hispanic, and American Indian/Alaskan Native children have a somewhat poorer outcome than white children. Asian/Pacific Islander children fare slightly better than white children. Although the reasons are not known, these differences may be the result of either host or leukemia characteristics.

Kadan-Lottick NS, Ness KK, Bhatia S, et al. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. *JAMA.* 2003;290(15):2008–2014.

KEY POINTS: HIGHER-RISK GROUPS WITH POORER PROGNOSIS OF PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

1. Age: $<$1 year and $>$10 years
2. White blood cell count: $>$50,000/mm^3
3. Chromosomal translocation abnormalities, specifically t(8;14), t(9;22), and t(4;11)
4. Hypoploidy ($<$45 chromosomes)
5. Malignant cells, with mature B-cell or T-cell immunophenotyping
6. CNS involvement
7. Black and Hispanic patients
8. Males

71. Although many prognostic factors have come and gone for childhood ALL, which two have remained significant for the past 50 years?

The two most consistent prognostic factors are **age** and **elevation of presenting white blood cell count**. Prognostic factors are important because although 95% of ALL patients achieve remission (defined as <5% lymphoblasts in bone marrow), 25% do relapse. Identifying patients at higher risk is important so that more aggressive or novel therapy can be considered.

72. In the United States, what are the four most common types of pediatric leukemia, and about how many children are diagnosed each year with each type?

ALL is most common, with about 2500 new diagnoses yearly; **AML**, with about 500 new diagnoses yearly; **chronic myelogenous leukemia** (CML), with about 100 new diagnoses yearly; and **juvenile myelomonocytic leukemia** (JMML), with about 50 new diagnoses yearly.

73. What other differential diagnoses should one consider when presented with pancytopenia and clinical findings suggestive of ALL?

- Aplastic anemia
- Bone marrow failure syndrome
- Viral- or drug-induced myelosuppression
- Metastatic disease to the bone marrow
- HLH
- HIV infection

74. What is MRD and how is it used?

MRD stands for *minimal residual disease,* which is typically detected by flow cytometry at several time points during therapy. In ALL, MRD detects patients who have a normal-appearing bone marrow by light microscopy, but in fact have an increased risk for relapse due to low-level, persistent disease. MRD is now known to be an important prognostic factor for outcomes in children with ALL and is used to help guide treatment. MRD use in AML is not as well defined as in ALL.

Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood.* 2008;111(12):5477–5485.

75. What are the most common sites of extramedullary relapse of ALL?

The most common is the **meninges**, and this is followed by **testicular relapse**. Testicular disease is accompanied by painless testicular swelling (usually unilateral). The diagnosis must be confirmed by biopsy. Patients with testicular disease require irradiation in addition to intensive retreatment with chemotherapy.

76. What is the role of cranial radiation in leukemia treatment?

The addition of prophylactic cranial radiation therapy to systemic therapy decreases the CNS relapse rate in ALL; however, it has significant side effects, including cognitive impairment, endocrine dysfunction, growth abnormalities, and secondary malignancies. Due to these significant negative effects, treatment now emphasizes intensified systemic and intrathecal chemotherapy rather than radiation for children without CNS disease at diagnosis.

Sison EA, Silverman LB. CNS prophylaxis in pediatric acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program.* 2014;2014(1):198–201.

77. What are the three phases of chemotherapy treatment for children with ALL?

1. **Remission induction**: The goal of this phase is to achieve a complete remission of disease.
2. **Intensification/consolidation**: The goal of this phase is to further eliminate any remaining leukemic cells that may not be detectable to prevent any relapse.
3. **Maintenance/continuation**: The goal of this phase is to further eliminate any residual leukemic cells using lower doses of anticancer drugs and to maintain remission for longer periods.

78. What are known risk factors for ALL?

Generally accepted risk factors include Down syndrome (10 to 20 times the risk compared with those without Down syndrome), Fanconi anemia, ataxia-telangiectasia, Schwachman-Diamond syndrome, Bloom syndrome, and previous chemotherapeutic treatment (e.g., cyclophosphamide, doxorubicin). Increased risk from ionizing radiation in utero remains unclear. Of note, long-term breastfeeding is suggestive of a decreased risk.

79. What are the clinical features and outcomes of transient myeloproliferative disorder (TMD) among newborns with trisomy 21?

Between 4% and 10% of newborns with trisomy 21 develop *TMD,* a rare and transient abnormal myelopoiesis, which has also been called *transient leukemia*. Clinical manifestations, ranging from asymptomatic to life threatening, involve infiltrative disease primarily of the liver, spleen, bone marrow, and skin. Although the majority of TMD cases undergo spontaneous remission within 3 to 7 months of age, about 20% progress to AML. AML can occur even after spontaneous resolution of TMD. Unlike AML in other children, however, children with trisomy 21 and AML have an excellent prognosis. Although most children are managed with supportive care, chemotherapy may be initiated earlier if there is life-threatening hyperleukocytosis, liver failure, hydrops, pericardial or pleural effusions, or a bleeding diathesis.

80. How is the treatment of acute promyelocytic leukemia (APL) different than for the other AML subtypes?

APL is a rare subtype of *AML* with a classic translocation t(15;17). The treatment of APL includes the administration of a vitamin A analog, all-trans-retinoic acid (ATRA), which induces differentiation of blast into more mature neutrophils. This treatment has dramatically increased survival for patients with APL.

81. What is a chloroma?

A *chloroma* is a tumor that is formed by a coalescence of AML blasts. It may appear in bones, skin, soft tissue, or other sites. Its name is derived from its green appearance on its cut surface.

82. What are the two major classes of lymphomas?

Lymphomas can be divided into **Hodgkin** and **NHL**. Lymphomas as a group are the third most common pediatric malignancy, with NHL accounting for approximately 7% of pediatric cancers. Whereas lymphomas in adults generally are defined as low grade or intermediate, almost all lymphomas in pediatrics are high grade. Higher-grade lymphomas are faster growing and more aggressive.

83. What is the malignant cell of Hodgkin disease?

The **Reed-Sternberg cell**. Its normal cell of origin remains unclear, with the predominance of evidence indicating a B or T lymphocyte. However, the cells alone are not pathognomonic of Hodgkin disease and may be seen in infectious mononucleosis, NHL, carcinomas, and sarcomas. A classic Reed-Sternberg cell has a bilobed or polylobed nucleus, which, when the two nuclear lobes are facing each other, gives the appearance of an "owl eye" (Fig. 14.5).

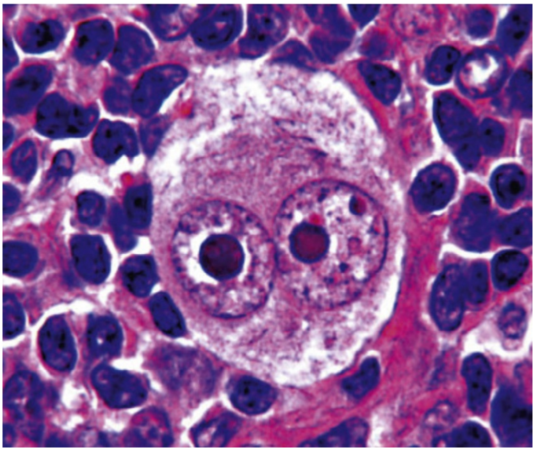

Fig. 14.5 Reed-Sternberg cell. (From Goldblum JR, Lamps LW, McKenney JK, Myers J, eds. *Rosai and Ackerman's Surgical Pathology.* 11th ed. Philadelphia, PA: Elsevier; 2018:1563.)

84. What is the staging system for Hodgkin disease?

The Ann Arbor staging system with Cotswolds modifications is the current staging system for Hodgkin lymphoma. Individuals are defined as being in one of four different numeric stages (stages I to IV):

- **Stage I**: Involvement of a single lymph node region; 19% of cases
- **Stage II**: Involvement of two or more lymph node regions on the same side of the diaphragm; 49% of cases
- **Stage III**: Involvement of lymph node regions on both sides of the diaphragm; 19% of cases
- **Stage IV**: Diffuse or disseminated disease; 13% of cases

85. How is Hodgkin lymphoma risk stratified?

Hodgkin lymphoma is risk-stratified according to **stage, bulky disease,** and **presence** or **absence of B symptoms**. Bulky disease describes the presence of a mediastinal mass that is more than one-third of the thoracic diameter or an extramediastinal node that measures >6 cm. "A" and "B" designations denote the absence or presence of B symptoms, which include one of the following: fever, night sweats, or unexplained weight loss >10% in the preceding 6 months.

86. What is the histologic classification of Hodgkin disease?

See Table 14.4.

Table 14.4 The Rye, New York, Histologic Classification[*]

TYPE	LYMPHOCYTES	REED-STERNBERG CELLS	OTHER	INCIDENCE (%)
Lymphocyte predominant	Many	Few	Histiocytes	10-15
Nodular sclerosing	Many	Few or many	Bands of refractile fibrosis	40-70
Mixed cellularity	Many	Few or many	Eosinophils, histiocytes	20-30
Lymphocyte depletion	Few	Many	No refractile fibrosis	<5

[*] Based on the relative number of lymphocytes and Reed-Sternberg cells.

87. What viral infection may play a significant role in the pathogenesis of Hodgkin disease?

EBV has been implicated in the development of Hodgkin disease. EBV positivity among Hodgkin disease varies by geography, patient ethnicity, histologic subtype, and age. It is most commonly observed in mixed cellularity (>50% cases) and lymphocyte-depleted subtypes.

88. What is the prognosis for the various stages of Hodgkin disease?

In general, the prognosis is excellent, in that most children are cured. For stages I and IIA, the 5-year relapse-free survival rate is >80% for patients treated with radiation only, and it may be >90% for patients treated with radiation and chemotherapy. For stage IIB, prognosis is not as good, especially if there is a massive mediastinal tumor, but 5-year survival is still >80%. The same survival figures pertain to stage IIIA disease, but treatment generally is more extensive than that for a limited stage II disease. For stage IV disease, the 5-year relapse-free survival rate is 70% to 90%.

89. How is childhood NHL classified?

The 2008 World Health Organization (WHO) system for classification is the one most commonly used. It relies on (1) **cell immunophenotype** (i.e., B lineage, T lineage, or NK lineage) and (2) **differentiation** (i.e., precursor versus mature cell). Although a large number of subtypes are categorized on the basis of histology and genetic studies, NHL of childhood and adolescence falls into three main categories, which are based in large measure on the clinical features and the therapeutic response to treatment. Long-term survival ranges from 70% to >95%.

- **Mature B-cell NHL** (Burkitt and Burkitt-like lymphoma/leukemia and diffuse large B-cell lymphoma): These account for about 40% to 50% of U.S. NHL pediatric cases.
- **Lymphoblastic lymphoma** (primarily precursor T-cell lymphoma and, less frequently, precursor B-cell lymphoma): These account for about 20% of U.S. cases.
- **Anaplastic large cell lymphoma** (mature T-cell or null cell lymphoma, which lacks characteristic markers of both T and B cells): These account for about 10% of U.S. cases.

Jaffe ES, Harris NL, Stein H, et al. Introduction and overview of the classification of the lymphoid neoplasms. In Swerdlow SH, Campo E, Harris NL, et al, ed. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2008:157–166.

90. Are there specific chromosomal abnormalities in Burkitt lymphoma?

Yes. Burkitt lymphoma is associated with three chromosomal translocations, resulting in the inappropriate expression of the c-Myc oncogene. The translocations are t(8;14) (most frequent) and t(8;22) or t(2;8) (relatively rare), each of which juxtaposes the c-Myc gene located on chromosome 8 (specifically, 8q24) with an immunoglobulin heavy-chain locus regulatory element. C-Myc is a proto-oncogene, which is involved in cellular proliferation.

91. What is the classic histology of Burkitt lymphoma?

A classic "starry-sky" pattern is usually present, due to numerous benign macrophages (histiocytes) that have ingested apoptotic tumor cells. The benign histiocytes (the stars) are large with abundant cytoplasm, dispersed evenly throughout a background of basophilic tumor cells (the sky). See Fig. 14.6.

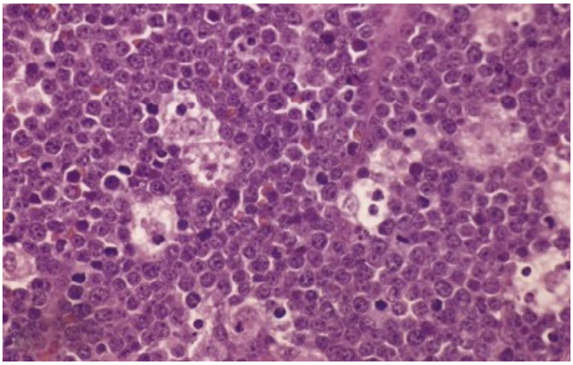

Fig. 14.6 Burkitt lymphoma histology. At low power, numerous pale tingible body macrophages are evident against a background of tumor cells, which produces a "starry sky" appearance. (From Kumar V, Abbas AK, Aster JC, eds. *Robbins and Cotran Pathologic Basis of Disease.* 9th ed. Philadelphia, PA: Saunders/Elsevier; 2015:600.)

92. What is the role of geography in the classification of Burkitt lymphoma?

The rapid onset of Burkitt lymphoma and its uneven geographic distribution have suggested a possible infectious etiology by a vectored pathogen as key to the disease. This peculiar epidemiology led the WHO to classify Burkitt lymphoma into three clinical entities: **endemic** (found primarily in countries where malaria is endemic, such as Africa and Papua New Guinea), **sporadic** (the predominant type found in the United States and in nonmalarial areas), and **immunodeficiency related** (seen most often in individuals with HIV). Each entity has different clinical presentations and genetic features. The endemic variant most commonly presents as a jaw or facial bone tumor, whereas the sporadic form has an abdominal presentation with ascites. EBV is found to be associated with almost all cases of the endemic variant, less frequently so with the immunodeficiency variant, and rarely in the sporadic variant.

Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. *Lancet.* 2012;379(9822):1234–1244.

93. Who was Burkitt?

Denis Burkitt was an Irish surgeon who, while living in Uganda, noted a series of children with swellings at the angles of the jaw and began to investigate the tumors. He published his case series in 1958, concluding that these represented a new, previously unrecognized tumor complex. He later became a prominent proponent of increased dietary fiber, having noted that many Western diseases were rare in Africa. He was one of the first to suggest a fiber-depleted etiology for colorectal cancer, although subsequent epidemiologic studies did not support that hypothesis. He died in 1993 at the age of 82.

Smith O. Denis Parsons Burkitt (1911-93), Irish by birth, Trinity by the grace of God. *Brit J Haematol.* 2012;156(6):770–776.

94. What differentiates B- and T-cell precursor leukemia from lymphoma?

The **bone marrow blast percentage** is used to differentiate B- and T-cell precursor leukemia from lymphoma. If the bone marrow blast percentage is $\geq$25%, the diagnosis of leukemia is given. If the blast percentage is $<$25% and the patient has other sites of malignant disease, the diagnosis of lymphoma is given.

95. What is posttransplant lymphoproliferative disease (PTLD)?

PTLDs are lymphomas that occur after either a stem cell transplant or organ transplant. PTLDs are typically associated with EBV reactivation. PTLD in children is typically of B-cell origin and more common in solid organ transplant recipients than in stem cell transplantation recipients. Standard initial management includes the withdrawal or reduction of immunosuppression. If the patient remains refractory to initial interventions, chemotherapy is initiated.

NERVOUS SYSTEM TUMORS

96. How are brain tumors classified?

Brain tumors are typically classified on the basis of cell of origin and histology:

- **Glioma:** Arises from supportive tissue (astrocytes)
- **Ependymoma:** Arises from the ependymal cells that line the ventricles
- **Germ cell tumor:** Arises from totipotent germ cells
- **Medulloblastoma:** Arises from embryonal cells at the earliest stage of development
- **Rhabdoid:** Arises from an unknown cell type, likely a primitive stem cell

- **Craniopharyngioma:** Arises from embryonic precursors to the anterior pituitary gland

The international classification of human tumors published by the WHO was initiated in 1957, and its goal has been to clearly define the classification and grading of tumors for worldwide acceptance and use. The sixth version of the WHO CNS classification system was published in 2016. It presents major restructuring of several brain tumor entities (diffuse gliomas, medulloblastomas) and incorporates new entities that are defined by both histology and molecular features (e.g., IDH mutation, H3 K27M mutation, RELA fusion).

Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016;131(1):803–820.

KEY POINTS: CENTRAL NERVOUS SYSTEM TUMORS

1. Second most common neoplasm of childhood, after leukemia
2. Older children (>1 year): Most tumors are infratentorial (cerebellar or brainstem)
3. Younger children (<1 year): Most tumors are supratentorial
4. Gold standard for diagnosis: Magnetic resonance imaging (MRI) with and without gadolinium enhancement
5. Back pain, extremity weakness, and/or bowel and bladder dysfunction suggestive of spinal cord lesions or metastases

97. Where is the most common area for each tumor to occur?

- **Glioma:** Cerebellum and optic pathway (more commonly low grade); cerebrum or brainstem (more commonly high grade)
- **Ependymoma:** Fourth ventricle; less commonly the spinal cord
- **Germ cell tumor:** Pineal or suprasellar region
- **Medulloblastoma:** Midline of the cerebellum
- **Rhabdoid:** Posterior fossa
- **Craniopharyngioma:** Middle cranial fossa sellar region

  See Fig. 14.7.

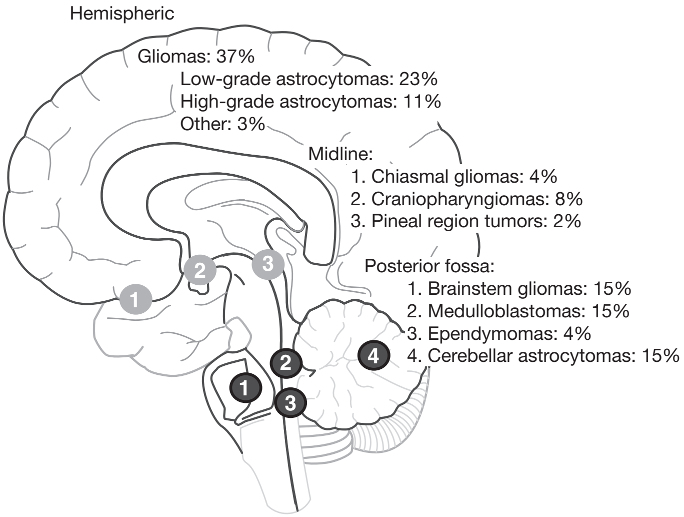
Hemispheric
Gliomas: 37%
Low-grade astrocytomas: 23%
High-grade astrocytomas: 11%
Other: 3%
Midline:
1. Chiasmal gliomas: 4%
2. Craniopharyngiomas: 8%
3. Pineal region tumors: 2%
Posterior fossa:
1. Brainstem gliomas: 15%
2. Medulloblastomas: 15%
3. Ependymomas: 4%
4. Cerebellar astrocytomas: 15%
1
2
3
1
2
3
4

Fig. 14.7 Relative frequency of brain tumor histologic types and anatomic distribution. (From Kleigman RM, Stanton BF, Schor NF, et al. *Nelson Textbook of Pediatrics.* 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:1748.)

98. What are the symptoms of supratentorial brain tumors?

Supratentorial tumors include tumors of the cerebrum, basal ganglia, thalamus, and hypothalamus. These tumors can show signs of increased intracranial pressure, such as morning headache or headache that goes away after vomiting. In addition, these tumors may be accompanied by focal deficits such as memory loss, weakness, visual changes, hearing, and speech problems. They can often present with seizure.

Hawley DP, Walker DA. A symptomatic journey to the centre of the brain. *Arch Dis Child Educ Pract Ed.* 2010;95(2):59–64.

99. What are the symptoms of infratentorial tumors?

Infratentorial tumors include tumors of the cerebellum and brainstem. If infratentorial tumors block CSF outflow, headache and vomiting may be the presenting signs; they can also become apparent with localizing signs such as cranial nerve palsies or ataxia (loss of balance and trouble walking).

100. Which cranial nerve abnormality is most common in children showing signs of increased intracranial pressure as the result of a posterior fossa tumor?

Inability to abduct one or both eyes **(cranial nerve VI palsy)** may result from an elevation in intracranial pressure and can be a false localizing sign for the primary brain tumor.

101. What are the symptoms of a spinal cord tumor?

Spinal tenderness on percussion correlates with the site of the tumor in up to 80% of patients. **Muscle weakness** or **numbness** in the arms or legs is also a common symptom. **Sensory-level changes** and **decreased reflexes** can also suggest a spinal cord compression. The collection of nerves at the end of the spinal cord is known the *cauda equina;* compression of these nerve roots can cause loss of bowel or bladder function and saddle anesthesia. Spinal cord compression most commonly occurs in the thoracic area (70%) compared with the lumbar (20%) and cervical (10%) regions.

102. What are the symptoms of diencephalic syndrome?

Diencephalic syndrome is the constellation of symptoms that result from the presence of a hypothalamic-optic chiasmatic tumor (in the diencephalon, located just above the brainstem). It is characterized by **failure to thrive** and **severe emaciation despite normal caloric intake**. Patients also have **hyperactivity** and **euphoria**, which is in contrast to their thinness and emaciation. Less commonly it may involve pallor without anemia, hypoglycemia, and hypotension.

103. What are the symptoms of posterior fossa syndrome?

Posterior fossa syndrome refers to a constellation of symptoms noted most commonly after surgery for posterior fossa tumors in the pediatric population. These signs and symptoms include **mutism** or **speech disturbances**, **dysphagia**, **decreased motor movement**, **cranial nerve palsies**, and **emotional lability**. These develop 1 to 4 days after surgery and may take weeks to several months to resolve.

104. What is Parinaud syndrome?

Parinaud syndrome is the result of **increased intracranial pressure at the dorsal midbrain**, causing downgaze, papillary dilation, and nystagmus.

105. What is a "drop metastasis"?

Most brain tumors do not metastasize; they are fatal because of local invasion. A *drop metastasis* occurs when a primary brain tumor spreads through CSF pathways, thereby resulting in meningeal deposits along the spinal cord. These metastases have "dropped" from their original site down to the spinal cord or cauda equina.

106. Why are epigenetic changes important in understanding brain tumors?

Cancer epigenetics most often refer to changes that affect gene activity and expression, causing phenotypic changes without alteration in the DNA sequence. In different types of cancers, an epigenetic change can cause silencing of a tumor suppressor gene or activation of an oncogene. DNA is usually wrapped around special proteins called *histones,* and changes in this packaging can influence the activity of the genes. The hallmark of diffuse intrinsic pontine glioma (DIPG) and diffuse midline glioma (both high-grade, aggressive tumors with poor prognosis) is a modification in the histone protein, which opens the DNA up, making it more vulnerable for mutations, and transforms normal neurons into cancerous cells. There has been an effort in recent years to develop drugs that would work through epigenetic pathways, with one of the most potent being the histone-deacetylase inhibitors.

Feinberg AP. The key role of epigenetics in human disease prevention and migration. *N Engl J Med.* 2018;378(14):1323–1334.
Kanwal R, Gupta K, Gupta S. Cancer epigenetics: an introduction. *Methods Mol Biol.* 2015;1238:3–25.

107. What are the prognostic factors for ependymoma?

Ependymoma arises from the inner lining of the ventricles. Several prognostic factors can help predict the outcome. Cranial location compared with primary spinal cord ependymomas, younger age at diagnosis, anaplastic histology, subtotal resection, and certain molecular characteristics (including chromosome 1q gain and RELA fusion) indicate a worse prognosis. Risk stratification based on these variables can guide management of ependymoma patients, optimizing the combination of treatment modalities.

108. What is the most common malignant brain tumor of childhood?

Medulloblastoma, which accounts for about 20% of all childhood brain tumors. Risk stratification is based on a number of factors, including extent of the disease (e.g., with or without metastasis), age at diagnosis (younger children, particularly <3 years, have a poorer prognosis), histopathology, and molecular markers. Analysis of molecular features not only helps in understanding the behavior of the tumor but also offers insight into the prognosis and provides an opportunity for individualized treatment. Medulloblastoma can be divided into four different molecular subgroups, with tumors that show activation of the Wnt pathway (a signaling pathway) having the best prognosis (group 1) and those with high-level amplification of the MYC proto-oncogene with aberrant MYC expression having the worst prognosis (group 3).

109. Which chemotherapeutic agents can be administered intrathecally to either treat or prevent meningeal malignancy?

Methotrexate, **cytarabine**, and **hydrocortisone** are commonly administered intrathecally to treat or prevent meningeal leukemia and lymphoma. **Thiotepa**, **etoposide**, and a novel formulation of **nitrosourea** (BCNU) are used for nonhematologic malignancies with meningeal involvement. Intrathecal chemotherapy has the advantage of delivering high drug concentrations to the CSF while minimizing systemic toxicities. Chemotherapy can be delivered through an Ommaya reservoir or while performing a lumbar puncture.

110. Which central and peripheral nervous system tumors are associated with neurofibromatosis (NF)?

NF, the most common cancer predisposition syndrome, has two main types. Each disease is associated with central and peripheral nervous system tumors. The *NF1* gene is located on chromosome 17, whereas the *NF2* gene is on chromosome 22. Both diseases are inherited in an autosomal dominant pattern. *NF1* can be associated with gliomas (most often, the optic nerve is involved), malignant peripheral nerve sheath tumor, and pheochromocytoma, while *NF2* is often accompanied by acoustic neurinoma (schwannoma), ependymoma, meningioma, or glioma.

Karajannis MA, Ferner RE. Neurofibromatosis-related tumors: emerging biology and therapies. *Curr Opin Pediat*. 2015;27(1):26–33.

111. What is leukocoria?

White pupillary reflex. It can be obvious, or it can be a subtle asymmetry on pupillary red reflex evaluation. Although other diagnoses can accompany leukocoria, the most significant one is retinoblastoma, which always needs to be ruled out when a child presents with leukocoria.

112. What is the difference between hereditary and sporadic retinoblastoma?

Although most cases are *sporadic,* retinoblastoma can be *inherited* as an autosomal dominant trait with nearly complete penetrance. Of all cases, 60% are nonhereditary and unilateral, 15% are hereditary and unilateral, and 25% are hereditary and bilateral. Retinoblastoma most often occurs in younger children, with 80% of cases diagnosed before the age of 5 years; hereditary retinoblastoma presents earlier than sporadic retinoblastoma. All retinoblastoma patients need genetic testing of the retinoblastoma *(Rb)* gene. Families should have genetic counseling. Patients with known *Rb* gene mutation need serial eye examinations starting at birth.

113. What is the “two-hit” hypothesis of cancer, particularly retinoblastoma?

Alfred Knudson’s “two-hit” hypothesis is a basic tenet of malignant transformation. In 1971, Knudson calculated the genetic probabilities of developing retinoblastoma and hypothesized that patients with bilateral disease first inherited a germline mutation and then underwent a second somatic mutation to develop the disease. Patients with unilateral or sporadic disease developed two somatic mutations during early childhood. The identification of the genes associated with the first of the “two hits” correctly predicted the presence of tumor suppressor genes.

Knudson A. Two genetic hits (more or less) to cancer. *Nat Rev Cancer.* 2001;1(2):157–162.

114. What are the principles of treating retinoblastoma?

Save the patient’s life first, save the eye second, save the vision the last. Depending on the size of the tumor and the extent of the disease, different combinations of surgery (cryotherapy, laser photocoagulation, enucleation), chemotherapy, and radiotherapy (plaque radiotherapy or external beam radiation) are recommended for treatment.

Abramson DH, Shields CL, Munier FL, Chantada GL. Treatment of retinoblastoma in 2015: agreement and disagreement. *JAMA Ophthalmol*. 2015;133(11):1341–1347.

115. What is the cell of origin of neuroblastoma?

Neuroblastoma is an **embryonal tumor** of the autonomic nervous system. The tumors originate in tissues of the sympathetic nervous system, most frequently in the adrenal medulla or paraspinal ganglia. Hence, neuroblastomas may present as mass lesions in the abdomen, pelvis, neck, or chest. Neuroblastomas are the most common solid extracranial tumor in children.

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KEY POINTS: NEUROBLASTOMA

1. Most common pediatric extracranial solid tumor
2. Most are sporadic, although 1–2% are hereditary
3. Majority of children <4 years old
4. Poorer prognosis: >1 year old, metastatic disease, Myc-N amplification
5. Most metastatic at diagnosis
6. Paraneoplastic syndromes: VIP syndrome (diarrhea as a result of increased vasoactive intestinal peptide [VIP]), opsoclonus-myoclonus (“dancing eyes, dancing feet”), and catecholamine excess (with flushing, sweating, headache, and hypertension)

116. What are the most common presentations of neuroblastoma?

Children with disseminated neuroblastoma are irritable and ill, and they often have exquisite bone pain, proptosis, and periorbital ecchymoses. Seventy percent of neuroblastomas arise in the abdomen; half of these arise in the adrenal gland, and the other half arise in the parasympathetic ganglia, with distribution throughout the retroperitoneum and the paravertebral area in the chest and neck. The tumor produces and excretes catecholamines, which can on occasion cause systemic symptoms such as sweating, hypertension, diarrhea, and irritability. Children with localized neuroblastoma may have symptoms referable to a mass.

Maris JM. Recent advances in neuroblastoma. *N Engl J Med.* 2010;362(23):2202–2211.

117. What is a Horner syndrome?

Ptosis, **miosis** (with unequal pupils), and **anhidrosis** (Fig. 14.8). The syndrome results from unilateral disruption of sympathetic neural pathways. The condition can occur from congenital brachial plexus injury, but acquired Horner

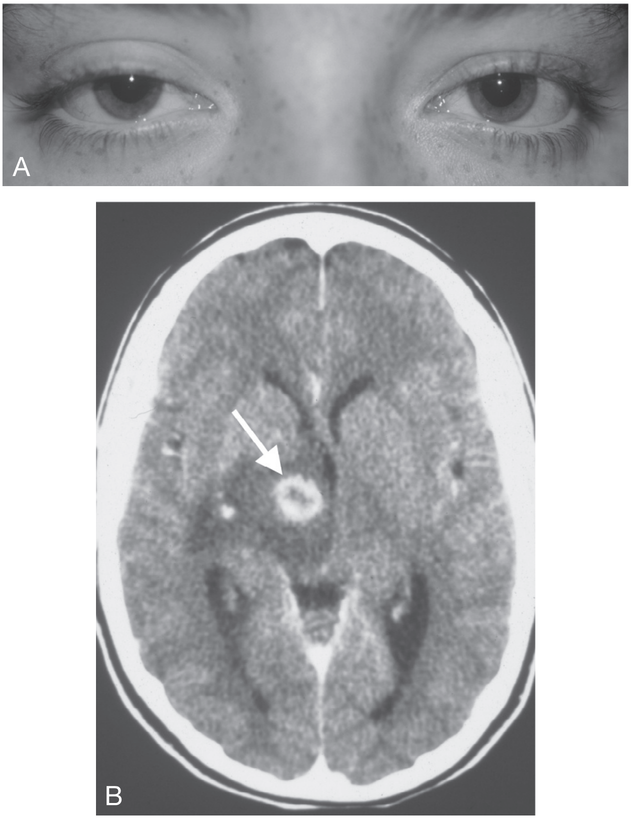

Fig. 14.8 (A) Right Horner syndrome due to a T-cell lymphoma involving the right thalamus and hypothalamus. (B) Ring enhancement *(arrow)* and edema are seen on the axial CT scan. (From Liu GT, Volpe NJ, Galetta SL, eds. *Neuro-Ophthalmology: Diagnosis and Management.* 2nd ed. Philadelphia, PA: Elsevier; 2010:431.)

syndrome requires evaluation for intrathoracic (preganglionic), cervical (postganglionic), or intracranial (central) pathology, particularly neuroblastoma.

118. What is meant by “dancing eyes, dancing feet”?

“Dancing eyes, dancing feet” is a descriptive term for **opsoclonus-myoclonus**, a condition in which children with neuroblastoma develop horizontal nystagmus and involuntary lower extremity muscle spasm. These symptoms are thought to arise from a nonspecific antibody reaction to neuroblastoma that cross-reacts with the motor end plate. These symptoms do not always improve despite appropriate neuroblastoma therapy with steroids, intravenous immunoglobulin (IVIG), or rituximab.

119. What does the S stand for in stage 4S neuroblastoma?

Stage 4S is a “special” type of neuroblastoma that is found only in children <1 year of age. Along with a primary tumor, these infants may have bone marrow, liver, and skin disease. Even without therapy, these cancers spontaneously regress and disappear over time. Treatment is only indicated if the patient is symptomatic from the underlying disease (e.g., large abdominal mass, liver disease).

120. Which molecular abnormality is associated with a more aggressive form of neuroblastoma?

MYCN amplification (increased copies of the *MYCN* gene in a patient’s DNA) is often seen in patients with stage 4 neuroblastoma. The presence of MYCN amplification renders a patient at higher risk for recurrence, regardless of staging, so they require more aggressive treatment. Other prognostic factors include age at diagnosis, stage, histologic characteristics, and chromosomal aberrations.

Ahmed AA, Zhang L, Reddivalla N, Hetherington M. Neuroblastoma in children: update on clinicopathologic and genetic prognostic factors. *Pediatr Hematol.* 2017;34(3):165–185.

121. What nuclear medicine agent has been useful in both the diagnosis and treatment of neuroblastoma?

^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) was developed at the University of Michigan in the 1970s for use as an antihypertensive agent. It is structurally similar to norepinephrine and found to concentrate within the neurosecretory granules of catecholamine-producing cells. In the 1980s, studies confirmed the usefulness of I-MIBG in localizing neuroblastoma; 90% of neuroblastomas have uptake of I-MIBG in both primary and metastatic sites. In the late 1980s, studies investigating the use of I-MIBG as a therapeutic modality came about and are currently still ongoing.

Swift CC, Eklund MJ, Kraveka JM, Alazraki AL. Updates in diagnosis, management and treatment of neuroblastoma. *Radiographics.* 2018;38(2):566–580.

122. What urinary test aids in the diagnosis of neuroblastoma?

Urinary concentrations of catecholamines and metabolites, including dopamine, homovanillic acid, and vanillylmandelic acid, are often increased (>3 standard deviations above the mean per milligram creatinine for age) in children with neuroblastoma.

SOLID NON–NERVOUS SYSTEM TUMORS

123. What are the peak ages of incidence of the most common solid tumors of childhood?

Neuroblastoma and Wilms tumor are tumors of *early childhood.* Ewing sarcoma and osteosarcoma are more prevalent during *adolescence*. Rhabdomyosarcoma *occurs throughout childhood and the teenage years.*

124. What congenital syndromes are associated with Wilms tumor?

- **WAGR syndrome**, defined as **W**ilms tumor, **A**niridia, **G**enitourinary malformations, and mental **R**etardation. It is associated with 11p13 loss of heterozygosity.
- **Beckwith-Wiedemann syndrome**, which is characterized by macroglossia, organomegaly, abdominal wall closure defects, and hemihypertrophy. It is associated with loss of imprinting at 11p15.
- **Denys-Drash syndrome**, which is characterized by nephropathy and male pseudohermaphroditism. It is due to a germline point mutation in the *WT1* gene.

125. What are the presenting symptoms for Wilms tumor?

Children often present with an **upper abdominal mass**, **abdominal pain**, **hematuria**, **hypertension**, and **anemia**. The average age of diagnosis is 3 to 4 years, with two-thirds of cases diagnosed <5 years. It is important not to palpate the abdomen too deeply on physical examination, as the tumor capsule may rupture, with tumor spillage. This will increase the tumor staging, which affects treatment decisions and long-term outcomes.

126. What are the three histologic components of a Wilms tumor?

Wilms tumors are considered triphasic, consisting of a **blastemal** (immature) component, an **epithelial** (tubular) component, and a **stromal** (muscular) component.

127. How is Wilms tumor distinguished radiographically from neuroblastoma?

- *Wilms tumor:* CT images will show intrinsic distortion of the kidney parenchyma and the collecting system. Only 10% of children with Wilms tumor have calcifications.
- *Neuroblastoma:* This is almost always extrarenal and causes displacement—not distortion—of the renal parenchyma and collecting system. Calcifications are seen in more than 50% of children with abdominal neuroblastoma.

128. Where does Wilms tumor tend to metastasize?

Locally, Wilms tumor can grow through the renal capsule, invade the renal veins, extend into the vena cava, and even progress into the chambers of the heart. The **lungs**, **regional lymph nodes**, and **liver** are the most common sites of metastasis.

129. How is Wilms tumor staged?

Tumor staging is **anatomically based**. Prognosis with bilateral disease is not necessarily poor.

- **Stage 1**: tumor confined to kidney
- **Stage 2**: tumor confined to the renal fossa
- **Stage 3**: gross postoperative residual disease confined to the abdomen
- **Stage 4**: disseminated tumor
- **Stage 5**: bilateral tumor involvement

130. What factors influence the prognosis of a patient with Wilms tumor?

Overall, Wilms tumor carries a good prognosis. Factors that influence the prognosis include tumor stage and histology, as well as chromosomal abnormalities such as **loss of heterozygosity (LOH)**. LOH for markers on the distal arm of chromosome 16 has been found in about 20% of Wilms tumors, whereas loss of the short arm of chromosome 1 has been found in about 10% of cases. LOH of either locus portends an adverse prognosis, independent of tumor stage and histology.

131. "Small, round, blue cell tumor" is often used in the description of which childhood tumors?

Neuroblastoma, **rhabdomyosarcoma**, **Ewing sarcoma**, **lymphoblastic leukemia**, and **lymphoma**. All appear as small, round, blue cells on low-power microscopic examination. High-power microscopic examination, usually in combination with a panel of immunohistochemical stains and molecular diagnostics, is required for definitive diagnosis.

132. Where are the most common primary locations of Ewing sarcoma, and where are the two most common sites of metastasis?

Pelvis, leg, upper arm, and rib are the *primary sites.* These tumors arise in extraskeletal (soft tissue) locations and can locally invade the bone. Ewing sarcoma often *metastasizes* to the **lungs** and somewhat less frequently to **other bones**. In general, lymph nodes are not involved, which suggests that dissemination of this tumor is primarily hematogenous.

133. What molecular abnormality is commonly seen in Ewing sarcoma?

The **t(11:22) translocation** is pathognomonic of Ewing sarcoma. This translocation results in the fusion gene *EWS-FLI1,* which is thought to disrupt transcriptional regulatory pathways. About 85% of Ewing sarcomas carry this translocation.

134. What are the classic radiographic features for osteosarcoma and Ewing sarcoma?

- *Osteosarcoma* typically has a "sunburst" or "hair on end" pattern on x-ray (Fig. 14.9A), which is due to its rapid growth, with the periosteum stretched and connected to bone via tiny ossified fibers.
- *Ewing sarcoma* has a lytic, "onion skin" or laminated pattern on x-ray (Fig. 14.9B) as concentric shells of new bone are layered intermittently as the lesion expands. Cortical destruction and periosteal reaction in both these aggressive bone lesions can result in "Codman triangle" in which the edges of raised subperiosteum ossify and form a small angle with the surface of the bone.

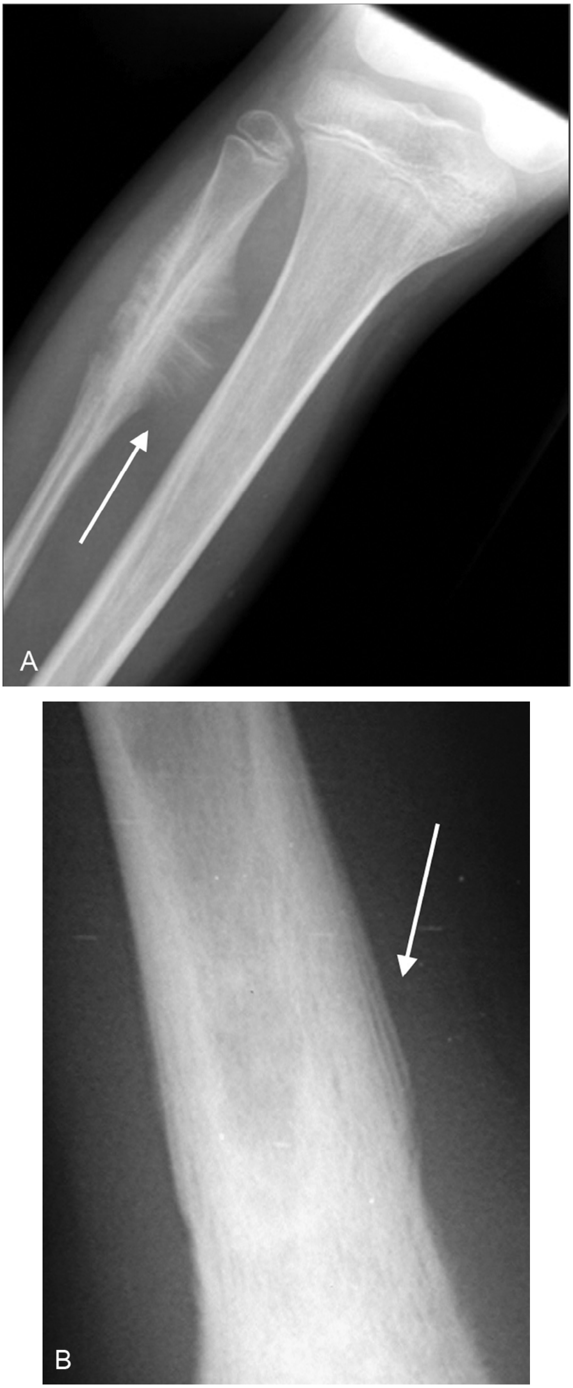

Fig. 14.9 (A) Osteosarcoma. Note aggressive lesion of proximal fibula with sunburst or "hair-on-end" periosteal reaction *(arrow)*. (From Torigian DA, Ramchandani P, eds. *Radiology Secrets Plus.* 4th ed., Philadelphia, PA: Elsevier; 2017:541.) (B) Ewing sarcoma. Note the "onion skin" showing multiple delicate layers of periosteal reaction surrounding the distal humerus *(arrow)*. (From Folpe AL, Inwards CY, eds. *Bone and Soft Tissue Pathology.* Philadelphia, PA: Elsevier Saunders; 2009:370.)

135. What is the histology of osteosarcoma?

An osteosarcoma is a **malignant spindle cell tumor** in which the cells produce neoplastic osteoid. It is the most common primary malignancy of bone in children.

136. Osteosarcoma generally arises in which part of the bone?

The **metaphyses** of long bones of the extremities. Between 60% and 80% of tumors are located in the metaphyses of the knee (i.e., the proximal tibia or the distal femur).

137. Do all patients with osteosarcoma require surgical resection of the primary tumor?

Surgical resection of the primary tumor is a requirement for curative treatment of osteosarcoma. In contrast to Ewing sarcoma, osteosarcoma is a relatively radiation-resistant tumor, and thus surgical resection after **neoadjuvant chemotherapy** is a mainstay of treatment.

138. For patients with localized osteosarcoma, what factor is most predictive of a favorable outcome?

Patients with **>95% necrosis** of the primary tumor (as determined by pathologic examination) after neoadjuvant chemotherapy have a better prognosis than those with lesser amounts of necrosis.

139. In addition to surgical resection, what chemotherapeutic agents are mainstays of treatment for osteosarcoma?

High-dose methotrexate, **doxorubicin**, and **cisplatin**. Both ifosfamide and etoposide have been trialed but have not been shown to have any increased efficacy and do have increased toxicity. Although novel therapies are currently being studied, there have been very few successful additions to therapy for osteosarcoma over the past approximately 30 years. Survival rates have been essentially unchanged during this period.

Bishop MW, Janeway KA, Gorlick R. Future directions in the treatment of osteosarcoma. *Curr Opin Pediatr.* 2016;28(1):26–33.

140. What benign tumors are in the differential diagnosis for bone tumors?

- **Osteochondroma**, which is asymptomatic and often occurs in metaphysis of long bones. It occurs in children between the ages of 5 and 15 and rarely transforms into malignant chondrosarcoma.
- **Osteoid osteoma**, which is characterized by recurrent, worsening pain, typically at night, and relieved by nonsteroidal anti-inflammatory drugs (NSAIDs). It is treated by removing the lesion.

141. What is a limb salvage procedure?

In an attempt to save as much natural tissue as possible, patients with soft tissue sarcomas often undergo a “limb salvage” surgery, in which cancerous tumor is removed from the bone without amputation. Because of the proximity of osteosarcomas to the knee joint, this often results in the removal of the joint as well. Patients who undergo a limb salvage procedure will require a prosthesis or crutches to ambulate.

142. What type of tumor is a rhabdomyosarcoma?

A *rhabdomyosarcoma* is a soft tissue tumor that arises from cells that give rise to striated skeletal muscle. It is the most common soft tissue tumor of childhood.

143. Where do rhabdomyosarcomas usually arise?

The four most common areas are as follows: (1) **head and neck**, (2) **genitourinary region**, (3) **extremities**, and (4) **orbit**. The survival rate for those with tumors in other areas is dependent on the amount, if any, of tumor left after resection and the presence or absence of metastatic disease.

144. What sites of disease are associated with the best outcomes for children with rhabdomyosarcoma?

Favorable locations include the orbit, the head and neck (except for parameningeal tumors), the vagina, and the biliary tract. *Unfavorable* locations include the extremities, retroperitoneum, and trunk.

145. What are the two major histologic subtypes of rhabdomyosarcoma?

Alveolar rhabdomyosarcoma, a name derived from its superficial appearance histologically to lung tissue, tends to occur in older children and adolescents. Most of these tumors carry the t(2;13) translocation, as well as a higher risk for recurrence. **Embryonal** rhabdomyosarcomas tend to occur in younger children and are the predominant histology associated with favorable-site tumors.

146. Which germ cell tumor is usually seen in young children?

Benign teratomas, typically occurring in the sacrococcygeal region. In general, patients with mature teratomas are managed by surgical resection. Care must be taken for sacrococcygeal tumors to be sure that the entire coccyx is removed.

147. Why are tumor markers assessed before surgery for teratomas and other germ cell tumors?

Tumor markers (e.g., α-fetoprotein, β-human chorionic gonadotropin [HCG]) are assessed in anticipation of postoperative monitoring for possible recurrence and malignant transformation. If elevated at diagnosis, these levels should be obtained monthly for the first 6 months because this is the highest risk period. If no elevation is noted, intermittent monitoring should be continued for a total of 3 years after resection.

148. Virilization may be associated with which childhood cancer?

Tumors that cause virilism are most commonly those that produce large quantities of dehydroepiandrosterone, a 17-ketosteroid. Tumors that produce testosterone may also cause virilization. Most commonly, these are **benign tumors of the adrenal gland**; rarely are they malignant. However, the distinction between carcinoma and benign adenoma is frequently difficult. Occasionally, males with primary hepatic neoplasms may become virilized because of the production of androgens by the tumor.

149. How great is the risk for malignant transformation in undescended testes?

Compared with baseline rates in adolescent and adult males, the risk for malignancy is approximately **three times higher** in the undescended testis than in a normal testis if surgery is done on a timely basis (between 6 and 18 months of age). The risk in the contralateral testis may also be increased. Orchidopexy decreases, but does not eliminate, the risk for subsequent malignant transformation.

Cho A, Thomas J, Perera R, Cherian A. Undescended testis. *BMJ.* 2019;364:1926.

Akre O, Petterson A, Richiardi L. Risk of contralateral cancer among men with unilaterally undescended testis: a meta-analysis. *Int J Cancer.* 2009;124(3):687–689.

Wood HM, Elder JS. Cryptorchidism and testicular cancer: separating fact from fiction. *J Urol.* 2009;181(2):452–461.

150. What are the most common primary liver tumors of childhood?

Hepatoblastoma and **hepatocellular carcinoma**. Hepatoblastomas usually develop in infants and young children, whereas hepatocellular carcinomas develop throughout childhood. Infection with hepatitis B and C virus is the greatest risk factor for the occurrence of hepatocellular carcinoma.

151. Which tumor marker is most likely to be elevated in children with hepatic tumors?

Most patients with either hepatoblastoma or hepatocellular carcinoma have an elevated concentration of **α-fetoprotein** that parallels disease activity. Lack of a significant decrease of α-fetoprotein with treatment may signify a poor response to therapy. Occasionally, hepatoblastomas produce **β-HCG** and can result in isosexual precocity.

152. Which histologic subtype of hepatoblastoma has the most favorable prognosis?

Fetal (most well-differentiated). The other subtypes of hepatoblastoma are embryonal/mixed fetal, macrotrabecular, and small-cell undifferentiated (which has a poor prognosis). The small-cell undifferentiated may also have a nonelevated serum α-fetoprotein, which confers a poor prognosis.

STEM CELL TRANSPLANTATION

153. What are the three main types of hematopoietic stem cell (HSC) transplant?

- **Allogenic:** The recipient receives stem cells from an HLA identical, haploidentical, or mismatched donor.
- **Autologous:** The donor and the recipient are the same person.
- **Syngeneic:** The donation is between identical twins.

154. What is the importance of HLA matching in HSC transplant recipients?

The genes for HLA, the major histocompatibility complex, are closely linked on chromosome 6. Matching donor and recipient for human leukocyte antigen (HLA) class I (A, B, and C) and class II (DRB1 and DQB1) haplotypes is vital to successful allogeneic HSC transplant. There is a progressive decrease in posttransplant survival with each HLA allele mismatch.

Fürst D, Müller C, Vucinic V, et al. High-resolution HLA matching in hematopoietic stem cell transplantation: a retrospective collaborative analysis. *Blood.* 2013;122(11):3220–3229.

155. What is the chance of siblings having the same HLA type?

The HLAs, which are located on chromosome 6, approximate simple mendelian inheritance, with two siblings having a 1 in 4 chance of having the same typing. A 1% crossover of material may also occur during meiosis. The larger the family, the more likely a match becomes, as shown by the formula $[1 - (0.75)^n]$, with n being the number of siblings. Thus a child with five brothers and sisters has a 76% chance of having a sibling with an HLA match.

156. What is the chance of finding an HLA-matched unrelated donor?

Although in theory the number of possibilities would equal or even exceed the world's population, thereby making a match astonishingly unlikely, HLA types cluster in individuals of similar genetic and racial backgrounds. In one estimate of persons of European ancestry, about 200,000 individuals would need to be screened to reach a 50% chance of finding a match.

Gahrton G. Bone marrow transplantation with unrelated volunteer donors. *Eur J Cancer.* 1991;27(12):1537–1539.

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157. What are the advantages and disadvantages of three methods by which stem cells are collected?

See Table 14.5.

Table 14.5 Methods of Collection for Stem Cells

STEM CELL SOURCE	METHOD OF COLLECTION	ADVANTAGES	DISADVANTAGES
Bone Marrow	Donor undergoes anesthesia, and bone marrow is collected from the donor by bone marrow aspirate	• High engraftment rates • Lower rates of chronic GVHD • Donor may be available to give a second transplant if needed	• Pain after harvest for donor • Donor size limits volume of marrow that can be harvested • Bone marrow has to be used fresh and cannot be stored • Coordination between donation and timing of transplant is critical and can be complex
Peripheral Blood	Donor receives G-CSF before donation to increase the number of peripheral blood stem cells and undergoes apheresis for stem cell collection	High engraftment rates	• G-CSF exposure can cause bony pain to the donor • Ongoing concern over long-term risks of G-CSF exposure to the donor (although there is no clear evidence of harm) • Donor may not be able to mobilize enough peripheral blood stem cells
Umbilical Cord Blood	Umbilical cord contains high numbers of hematopoietic stem cells at the time of delivery, so cord blood is often harvested from the placenta at the time of delivery	• HLA mismatching more permissive due to lower rate of GVHD • No risk to mother or infant • Available on demand after cryopreservation	• Higher rates of graft failure (slowest to engraft compared with bone marrow or peripheral blood) • Higher rates of viral infections • Limited number of stem cells in the collection • Possible lack of availability of additional donor cells if graft failure or relapse occurs • Undiagnosed medical condition may be present in newborns

G-CSF, Granulocyte-colony-stimulating factor; *GVHD*, graft-versus-host disease; *HLA*, human leukocyte antigen.

158. What is the rationale behind an autologous transplant?

Autologous transplants (stem cells from the patients themselves) are used in situations where high-dose chemotherapy will increase the response rate in chemosensitive tumors but toxicity from the intense chemotherapy is a limiting factor. This limitation can be overcome by harvesting HSCs from the patient, cryopreserving, and then subsequently reinfusing the HSCs after the patient received the chemotherapy and/or radiotherapy.

159. What are some indications for autologous transplant in children?

Autologous transplants are more routinely performed for children with high-risk neuroblastoma and certain types of relapsed lymphoma. Certain types of brain tumors also incorporate autologous transplant, especially in those patients who are <3 years old, to avoid or delay radiation therapy to the developing brain. There is also research evaluating the use of autologous transplant in children with solid tumors with high-risk features.

160. What are some nonmalignant indications for an HSC transplant?

The list of nonmalignant indications is growing, both for hereditary disorders that trace their origin to the HSC (e.g., sickle cell disease, thalassemia major) and, more recently, for nonhematopoietic hereditary disorders in which engraftment of stem cells might ameliorate damage in target organs. These latter diseases have included epidermolysis bullosa and Fanconi anemia.

Tolar J, Mehta PA, Walters MC. Hematopoietic cell transplantation for nonmalignant disorders. *Biol Blood Marrow Transplant.* 2012;18(1 Suppl):S166–S171.

161. In transplant medicine, to what does the term “conditioning” refer?

Conditioning refers to the preparative regimen necessary to achieve bone marrow ablation and immune suppression for successful donor engraftment to occur. This conditioning regimen, which can include chemotherapy and/or radiation, also serves as a disease therapy in allogenic stem cell transplant for malignant disease.

162. What are the three most common categories of conditioning regimens?

- **Myeloablative:** These are composed of single or combination agents that completely destroy the HSCs in a patient’s bone marrow. The result is severe pancytopenia that is often irreversible and may be fatal without the infusion of a stem cell rescue. Current myeloablative regimens may include total-body irradiation or high-dose busulfan.
- **Nonmyeloablative:** This causes minimal cytopenia (but severe lymphopenia) and does not require stem cell support.
- **Reduced intensity:** An intermediate category of regimens, which may lead to prolonged cytopenias (although not frequently irreversible) and may require stem cell infusion for support.

Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant.* 2009;15(12):1628–1633.

163. Do all transplant patients require complete ablation of their recipient bone marrow?

No. Stem cell transplants that do not ablate the recipient bone marrow are called *nonmyeloablative transplants*. Such transplants require vigorous immune suppression to maintain the donor graft, as well as a disease that does not require intensive chemotherapy or full donor engraftment for success. Thus patients with leukemias that respond well to a graft-versus-leukemia effect may benefit from the decreased morbidity and mortality of a reduced-intensity preparative regimen.

164. What are the major side effects from total-body irradiation used in conditioning?

In the short term, total-body irradiation may cause **interstitial pneumonitis** and **nephritis**. Over the long term, total-body irradiation may lead to cataracts, growth retardation, hypothyroidism, other endocrine dysfunction, infertility, and secondary malignancies. The long-term effects of total-body irradiation on pulmonary, cardiac, and neuropsychiatric function continue to be studied.

165. Which prophylactic measures should be taken after stem cell transplantation?

Patients may receive antibiotics for gut decontamination. An oral antifungal agent such as fluconazole is also frequently administered. Patients should receive *P. jiroveci* prophylaxis and replacement of immunoglobulins with IVIG. Acyclovir may also be administered.

166. What is the pathophysiology underlying graft-versus-host disease (GVHD)?

Graft-versus-host disease is a multisystem disorder that can occur after stem cell transplant due to an immune reaction. In GVHD, after the transplant, donor T cells recognize the recipient’s body cells as foreign and initiate an inflammatory response in the recipient tissues.

167. Describe the clinical manifestations of acute and chronic GVHD

- *Acute GVHD* affects the skin, gastrointestinal (GI) tract, and liver. Skin problems manifest as rash, pruritus or, in its more severe form, bullous lesions and desquamation. GI tract features are usually nausea, vomiting, diarrhea, abdominal pain, and anorexia. Hepatic complications are jaundice, transaminase elevations, and bilirubin elevation.
- *Chronic GVHD* resembles an autoimmune-like syndrome, which can affect the eyes, mouth, skin, stomach, or liver. Clinical features include dry eyes and mouth and scaly skin with scarring, stiff joints, loss of weight and appetite, diarrhea, and jaundice.

168. Can we distinguish acute and chronic GVHD by time to onset?

Although acute GVHD typically occurs in the first 100 days after transplant and chronic GVHD after 100 days, timing of onset to define acute versus chronic is now more arbitrary because the clinical manifestations of each are better defined.

169. What is the significance of the grading of acute GVHD?

Grading of acute GVHD is based on percentage of BSA involved by the dermatitis, degree of hyperbilirubinemia, and volume of diarrhea. Grading is important to determine optimal treatment and to assess response to treatment. Patients with a higher grade (or moderate to severe forms) of GVHD have a significantly higher mortality rate than those with a mild form.

170. How is GVHD managed?

Doses of methotrexate, cyclosporine, or tacrolimus during the immediate posttransplantation period may be given in an attempt to prevent the development of acute GVHD. T-cell depletion of the bone marrow graft also decreases the incidence of GVHD. For the treatment of acute GVHD, steroids, cyclosporine, or tacrolimus may be used alone or in combination, depending on the extent of donor–recipient mismatch and the severity of GVHD.

Carpenter PA, MacMillan ML. Management of acute [illegible]t-versus-host disease in children. *Pediatr Clin North Am.* 2010;57(1):273–295.

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171. What are the risk factors for GVHD?

There are multiple risk factors for GVHD. First and foremost is the **relatedness of the donor to the recipient**. An unrelated donor transplant will have a higher risk for GVHD than a matched related donor transplant. Second, the **number of T cells received** is a risk factor, with higher T-cell numbers associated with a higher risk for GVHD. **Donor age** and **parity status** are also risk factors, with older donors and multiparous donors having higher risks of GVHD.

172. What is graft-versus-leukemia (GVL)?

GVL occurs when the donor marrow recognizes antigens on the leukemic blast cell as foreign and initiates immune-mediated clearance of the malignant cell. GVL is most easily obtained in patients who have been transplanted for CML, although patients with AML and ALL may also experience a GVL effect. Thus GVL constitutes an important part of the antileukemic effect of transplantation, particularly for CML and AML. Current research is directed at separating the detrimental GVHD effect from the beneficial GVL effect.

173. What is the most likely diagnosis for a patient who experiences weight gain, right upper quadrant pain, and hepatomegaly 10 days after stem cell infusion?

The patient most likely has **venoocclusive disease (VOD)**, also known as **sinusoidal obstruction syndrome (SOS)**. VOD/SOS is due to damage to the hepatic endothelial cells that then leads to activation of the clotting cascade within the hepatic sinusoids and subsequent reversal of blood flow through the liver. Severe VOD/SOS may be characterized by more than 10% weight gain, respiratory failure, hepatorenal syndrome, and mental status changes. The treatment of VOD centers on maintaining adequate intravascular volume without compromising respiratory function and administration of defibrotide.

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CHAPTER 15

ORTHOPEDICS

Benjamin D. Roye, MD, MPH

CLINICAL ISSUES

1. If a newborn infant is not moving one arm spontaneously, what could be the problem?

You need to determine whether the baby is not moving because he or she does not want to move a painful arm or cannot. If an infant is having pain, he or she will not want to move their arm, a condition called *pseudoparalysis*. This could be the result of an **injury** (such as a clavicle or humerus fracture) or, more seriously, due to an **infection** of the bone or joint of the shoulder. These infections should be considered an emergency, as the immune systems of infants are not fully developed, and they can have severe complications if not promptly treated. If a baby cannot move an arm without pain, a neurologic injury is likely preventing motion—most commonly a brachial plexus injury.

2. How can I tell the difference between a baby *not wanting* to move and *not being able* to move an arm?

Looking for the **presence of reflexes** can help distinguish a neurologic injury from a painful condition—the baby cannot stop the reflex arc and will move if the nerves are intact. Upper extremity reflexes in the infant include the grasping reflex, Moro (startle) reflex, and tonic neck reflex.

3. Are growing pains real?

Yes! *Growing pain* is an accepted diagnosis in children (typically $\leq$12 years) who complain of pain in one or both legs, usually in the evening or at night. Pain is typically more common on days of increased activity. At times the pain can awaken the child from sleep. The vast majority of children respond to measures such as ice or heat, massage, and acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). On the following morning, they are usually feeling fine. The symptoms should occur irregularly—from a few times a week to a few times a month. Symptoms that occur on a daily basis and/or interfere with activities during the day should be worked up for another possible diagnosis. Growing pains are also less likely if there are systemic symptoms or abnormal physical examination findings, such as allodynia (triggering of a pain response from a stimulus that normally does not elicit pain), focal tenderness, joint swelling, or decreased range of motion.

Lehman PJ, Carl RL. Growing pains. *Sports Health.* 2017;9(2):132–138.
Peterson H. Growing pains. *Pediatr Clin North Am.* 1986;33(6):1365–1372.

4. What is torticollis?

Torticollis, also called a *"cock-robin" deformity,* is a combined head tilt in one direction with rotation in the opposite direction (Fig. 15.1). This deformity may be fixed or flexible.

5. What is the differential diagnosis for torticollis?

Torticollis is a *symptom* that has a variety of underlying etiologies:

- **Osseous:** Atlanto-occipital anomalies, unilateral absence of C1, Klippel-Feil syndrome (fusion of cervical vertebrae), atlantoaxial rotatory displacement, basilar impression
- **Nonosseous:** Congenital muscular torticollis, Sandifer syndrome (severe gastroesophageal reflux), ocular dysfunction (strabismus, oculogyric crisis), infections (cervical adenitis, retropharyngeal abscess), central nervous system tumors, syringomyelia, Arnold-Chiari malformation, abnormal skin webs (pterygium colli)

Tomczak KK, Rosman NP. Torticollis. *J Child Neurol.* 2013;28(3):365–378.

6. Are stretching exercises helpful for congenital muscular torticollis?

Yes. *Congenital muscular torticollis* may present as postural preference only (no muscle tightness or restriction) or can have tightness of the sternocleidomastoid (SCM) muscle with restricted range of motion and, in many cases, a mass palpable in the SCM muscle. In congenital muscular torticollis, the head tilts toward and the chin rotates away from the involved SCM muscle. The condition is usually noted in the first few weeks of life. The etiology is unclear, although in utero injury to the SCM muscle with fibrosis has been proposed. Studies have shown that management with manual stretching—particularly when initiated at an early age—significantly reduces the need for surgical correction.

Kaplan SL, Coulter C, Sargent B. Physical therapy management of congenital muscular torticollis: a 2018 evidence-based clinical practice guideline from the APTA Academy of Pediatric Physical Therapy. *Pediatr Phys Ther.* 2018;30(4):240–290.
Suhr MC, Oledzka M. Considerations and intervention in congenital muscular torticollis. *Curr Opin Pediatr.* 2015;27(1):75–81.

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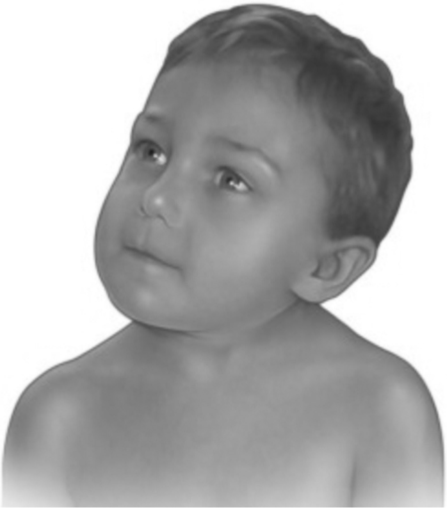

Fig. 15.1 Torticollis with lateral/side bending of the head toward the left and cervical/chin rotation to the right. (From Herring JA, ed. *Tachdjian's Pediatric Orthopedics*. 5th ed. Philadelphia, PA: Elsevier Saunders; 2014:487.)

7. An x-ray in a 15-year-old boy taken to rule out an ankle fracture reveals a well-circumscribed lytic lesion in the cortex of the tibia away from where he is having any symptoms. What is this likely to be?

There are a variety of incidental findings on x-ray that carry little clinical significance, sometimes called *incidentalomas*. The lesion described here could easily be a **nonossifying fibroma**, also called a *fibrous cortical defect* (Fig. 15.2). This is the *most common benign tumor* in childhood and typically resolves spontaneously. Very large lesions can rarely weaken the bone enough to pose a fracture risk, and a small percentage of these lesions present with a pathologic fracture.

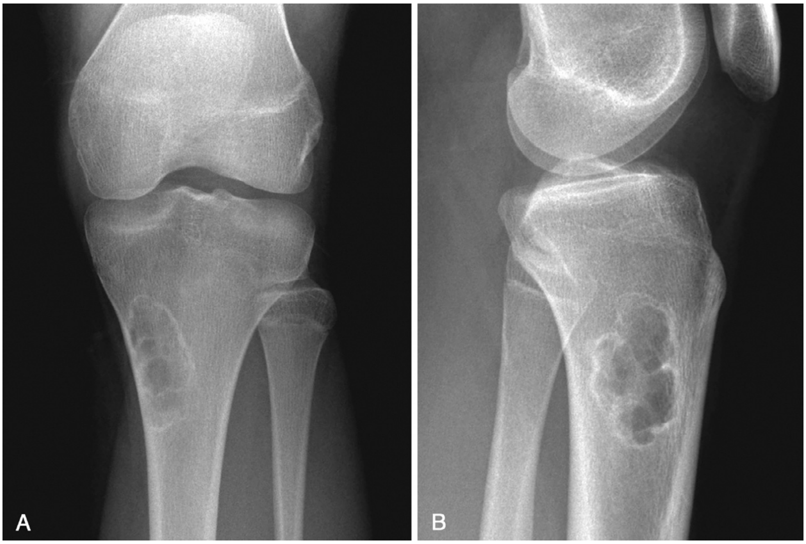

Fig. 15.2 Anteroposterior (A) and lateral (B) radiographs of nonossifying fibroma of proximal tibia in a 15-year-old. (From Azar FM, Beaty JH, Canale ST, ed. *Campbell's Operative Orthopedics*. 13th ed. Philadelphia, PA: Elsevier; 2017:907.)

8. What other common types of benign bone tumors are seen in children?

Unicameral bone cysts (UBCs) and **aneurysmal bone cysts (ABCs)**. These lesions tend to occur in the metaphyses of long bones and typically have a "bubbly" lytic appearance on x-ray, and they usually have well-defined borders, as they are slow growing. Both types of cysts are commonly treated with surgery to curettage out the cyst and placement of a bone graft to get the lesion to heal.

Mascard E, Gomez-Brouchet A, Lambot K. Bone cysts: unicameral and aneurysmal bone cyst. *Orthop Traumatol Surg Res.* 2015; 101(1 Suppl):S119–S127.

9. How can you differentiate between an ABC and a UBC, and does it matter?

Although the x-ray appearance of *ABCs* and *UBCs* can be very similar, on magnetic resonance imaging (MRI) you will see **fluid–fluid levels**, which are *pathognomonic for ABCs* and *will not be seen in UBCs* (which are sometimes called *simple cysts* for this reason). The fluid–fluid levels seen in ABCs represent the two fluids in the cyst: the cyst fluid and blood. It is important to differentiate between these two lesions before surgery! Although both lesions are benign, *ABCs* can be **locally aggressive** and have a **much higher recurrence rate**. *ABCs* are often associated with other tumors, including giant cell tumor, chondroblastoma, and fibrous dysplasia. As such, typically a more aggressive open surgery will be performed for an ABC, whereas less aggressive percutaneous procedures are often attempted for UBCs.

10. What is rickets?

Rickets is the failure of osteoid to calcify in a growing child, most commonly caused by a lack of vitamin D. The adult equivalent is osteomalacia.

Wharton B, Bishop N. Rickets. *Lancet.* 2003;362(9393):1389–1400.

11. Why is rickets reappearing?

There has been an increase in exclusive breastfeeding for prolonged periods without vitamin D supplementation. Human milk is low in vitamin D, and the American Academy of Pediatrics (AAP) recommends vitamin supplementation for breastfed infants. Additionally, reduced maternal sunlight exposure for cultural, societal, or personal reasons has become more common. Immigrant groups who have increasingly migrated to more temperate regions have more children with this condition; reasons remain unclear for the increased incidence among these groups.

Creo AL, Thacher TD, Pettifor JM, et al. Nutritional rickets around the world: an update. *Paediatr Int Child Health.* 2017;37(2):84-98.

12. What physical signs are suggestive of rickets?

The anatomic abnormalities of rickets result primarily from the inability to normally mineralize osteoid; the bones become weak and subsequently distorted. Signs of rickets include the following:

- Femoral and tibial bowing
- Delayed suture and fontanel closure
- Pectus carinatum, or "pigeon breast" (anterior protrusion of the sternum)
- Frontal thickening and bossing of the forehead
- Defective tooth enamel
- Harrison groove (a rim of rib indentation at the insertion of the diaphragm)
- Widened physes at wrists and ankles
- "Rachitic rosary" (enlarged costochondral junctions)

13. What is the most significant mistake made during the evaluation of knee pain?

Failure to evaluate the hip as a source of the pain. Hip pathology frequently masquerades as knee or distal thigh pain (e.g., Legg-Calvé-Perthes [LCP] disease, slipped capital femoral epiphysis). Just as a patient with a heart attack may complain of left arm pain, hip pain in children can be referred down the thigh. More than one knee has undergone a diagnostic arthroscopy for hip pathology. The mantra in pediatric orthopedics is "knee pain equals hip pain until proven otherwise."

14. Which bones are known to develop aseptic necrosis?

The **osteochondroses** are a group of disorders in which aseptic necrosis of epiphyses occurs with subsequent fragmentation and repair (Table 15.1). The exact cause is unknown in most cases. However, systemic steroid use has been associated with the development of aseptic necrosis, as have chronic diseases like sickle cell disease. The patient usually presents with pain at the affected site.

Danger F, Wasyliw C, Varich L. Osteochondroses. *Semin Musculoskeletal Radiol.* 2018;22(1):118–124.

15. What are the inheritance patterns and clinical features of osteogenesis imperfecta?

Of the several types of *osteogenesis imperfecta,* the most common is type IV, which occurs in 1 in 30,000 live births. The clinical features vary and depend on the severity of the condition (Table 15.2).

Table 15.1 Typical Age of Onset of Osteochondroses

LOCATION	EPONYM	TYPICAL AGE OF ONSET (YR)
Tarsal navicular bone	Köhler disease	6
Capitellum of distal humerus	Panner disease	9-11
Carpal lunate	Kienböck disease	16-20
Distal lunar epiphysis	Burns disease	13-20
Head of femur	Legg-Calvé-Perthes disease	3-5

Table 15.2 Types of Osteogenesis Imperfecta

TYPE	INHERITANCE	CLINICAL FEATURES
I	Autosomal dominant	Bone fragility, blue sclerae, onset of fractures after birth (most at preschool age)
Type A		*Without* dentinogenesis imperfecta
Type B		*With* dentinogenesis imperfecta
II	Autosomal recessive	Lethal in perinatal period, dark blue sclerae, concertina femurs, beaded ribs
III	Autosomal recessive	Fractures at birth, progressive deformity, normal sclerae and hearing

16. What are the causes of in-toeing gait (pigeon-toeing)?

In-toeing can be due to problems in the foot, tibia, or hip:

- **Foot:** Metatarsus adductus
  - Talipes equinovarus (clubfoot)
- **Leg:** Tibial torsion (internal)
- **Hip:** Femoral anteversion (medial femoral torsion)
  - Paralysis (polio, myelomeningocele)
  - Spasticity (cerebral palsy)
  - Maldirected acetabulum

Tunnessen WW Jr. *Signs and Symptoms in Pediatrics*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:693–695.

17. Is in-toeing a problem?

No. For the vast majority of cases, in-toeing is not a pathologic problem. There is a normal range of foot placement during gait that can range from slightly internally rotated to slightly externally rotated. Many children will improve their walking as they get older: most children do not have a mature gait pattern until around age 7. Many elite runners turn their feet in when running, as they are faster this way. Most parents love this piece of information.

Sielatycki JA, Hennrikus WL, Swenson RD, et al. In-toeing is often a primary care orthopaedic condition. *J Pediatr.* 2016;177:297–301.

18. When, if ever, does in-toeing need to be treated?

In-toeing rarely requires treatment other than reassurance to the family that their child's walking will improve with time. In addition, femoral anteversion and tibial torsion almost never require treatment in the neurologically normal child. Traditional treatments such as the infamous boots and bars and orthopedic shoes do nothing to change the natural history of these problems. Metatarsus adductus often spontaneously resolves in the first 2 years of life, but feet that are rigid (i.e., the foot cannot easily be manipulated into a normal position) or severe cases may require casting, straight-laced shoes, or, in extreme cases, surgery. Children with extreme rotational problems or very asymmetric rotation occasionally benefit from surgery to derotate the affected bone (tibia or femur).

19. A 15-year-old has tibial pain that is worse at night and greatly relieved by NSAIDs. X-rays show a small lytic area surrounded by reactive bone formation. What is the most likely diagnosis?

Osteoid osteoma, a benign bone-forming tumor, is typically seen in older children and adolescents and exhibits a male predominance (male-to-female ratio 2:1). Most children complain of localized pain, usually in the femur and tibia; however, the arms and vertebrae may also be involved. Radiographs may demonstrate an osteolytic area surrounded by densely sclerotic reactive bone, and bone scans reveal "hot spots." Computed tomography (CT) scans will show a "nidus" in the middle of the lesion, which is pathognomonic for this diagnosis (Fig. 15.3). The site is usually <1 cm in diameter and arises at the junction of the old and new cortex. Pathologically, the lesion is highly vascularized, fibrous tissue with an osteoid matrix and poorly calcified bone spicules surrounded by a dense zone of sclerotic bone. Treatment is surgical excision or thermal ablation.

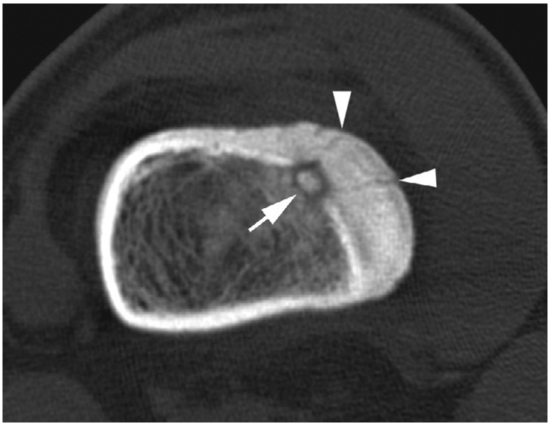

Fig. 15.3 Tibial osteoid osteoma. CT shows a densely mineralized intracortical nidus *(arrow)* with solid adjacent periosteal thickening containing multiple vascular channels *(arrowheads)*. (From Adam A, Dixon AK, Gillard JH, Schaefer-Prokop CM, eds. *Grainger & Allison's Diagnostic Radiology.* 6th ed. Philadelphia, PA: Elsevier; 2015:1099.)

20. What are the possible causes of a limb-length discrepancy?

- **Congenital anomalies**: Congenital short femur, proximal femoral focal deficiency, congenital absence of fibula, posteromedial bowing of tibia, tibial hypoplasia, congenital hemihypertrophy
- **Tumors**: Neurofibromatosis, fibrous dysplasia, enchondromatosis, hereditary multiple exostosis, Klippel-Trénaunay-Weber syndrome
- **Trauma**: Physeal injuries, fracture
- **Infection**: Septic arthritis, osteomyelitis (the infection can damage the growth plates)
- **Inflammatory**: Juvenile idiopathic arthritis

21. What are the long-term effects of uncorrected limb-length discrepancy?

Limp and **low-back pain** are the most common sequelae of a limb-length discrepancy, as the pelvic tilt places increased stress on the lumbosacral spine. Other complications in more severe cases can include an **equinus contracture of the ankle** and late **degenerative arthritis** of the hip.

22. What are the general management principles for a limb-length discrepancy?

- *0 to 2 cm*: No treatment
- *2 to 6 cm*: Shoe lift, epiphysiodesis
- *6 to 20 cm*: Limb lengthening
- *$>$20 cm*: Prosthetic fitting

There is flexibility in these guidelines to account for factors such as environment, motivation, intelligence, compliance, emotional stability, patient and parental wishes, predicted final height, and associated pathology in the limbs.

Friend L, Widmann RF. Advances in the management of limb length discrepancy and lower limb deformity. *Curr Opin Pediatr.* 2008; 20(1):46–51.

23. What is a nursemaid elbow?

Nursemaid elbow, sometimes *called pulled elbow,* is a **subluxation of the radial head under the annular ligament**, which results typically from axial traction applied to the extended arm of a young child (Fig. 15.4). A classic history is a parent lifting a child by the arm over an object or curb with the child then unwilling to move the affected limb (pseudoparalysis). On examination, there is tenderness directly over the radial head. Radiographs are normal, so the diagnosis must be made by history and physical examination.

24. How is a nursemaid elbow reduced?

Two methods can be utilized: **supination-flexion** and **hyperpronation**. In one, the subluxed radial head is reduced by supinating the extended forearm, followed by fully flexing the elbow. In the other, the forearm is hyperpronated. When there is a successful reduction, an audible and palpable click is often present. After

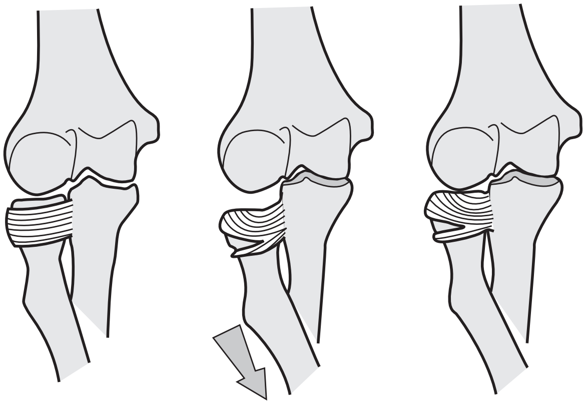

Fig. 15.4 Pathology of nursemaid elbow. When the arm is pulled, the radial head moves distally. When traction is discontinued, the ligament is carried into the joint. (From Kliegman RM, Stanton BF, Schor NF, et al, eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:2384.)

successful reduction, the child will begin to use their arm spontaneously (usually after a few minutes of crying). If symptoms persist, the child should be reassessed for a possible occult fracture of the radial head or distal humerus. Limited studies have found that the hyperpronation method may be more effective and less painful than the supination method as a technique for reduction.

Bexkens R, Washburn FJ, Eygendaal D, et al. Effectiveness of reduction maneuvers in the treatment of nursemaid’s elbow: a systematic review and meta-analysis. *Am J Emerg Med.* 2017;35(1):159–163.

25. How can you differentiate between osteomyelitis and osteonecrosis (i.e., bone infection vs. bone infarction) in patients with sickle cell disease?

This is an important distinction, as the treatments will be very different, but presentations can be very similar. An acute vaso-occlusive crisis leads to osteonecrosis and causes severe pain: it is one of the most common reasons for a child with sickle cell to present for medical care. Both infection and infarction can present with pain, fever, and elevated inflammatory markers. Standard radiographs are not very helpful, and MRIs can be confusing. However, **combining bone marrow scans and bone scans** has been found to be the most reliable way to differentiate between these two conditions: Bone infarction will have low uptake on marrow scan and abnormal bone scan in the same area. Infection will have normal marrow scan and normal bone scan in the same area.

Kosaraju V, Harwani A, Partovi S, et al. Imaging of musculoskeletal complications in sickle cell disease patients. *Br J Radiol.* 2017; 90(1073):20160130.

Skaggs DL, Kim SK, Greene NW, et al. Differentiation between bone infarction and acute osteomyelitis in children with sickle-cell disease with use of sequential radionuclide bone-marrow and bone scans. *J Bone Joint Surg Am.* 2001;83(12):1810–1813.

26. What constitutes an orthopedic emergency?

There are few true emergencies in orthopedics that require immediate attention, but conditions that fall into this category include open fractures, impending compartment syndrome, femoral neck fractures (including unstable slips of the proximal femoral physis or slipped capital femoral epiphysis [SCFE]), dislocation of major joints (i.e., knee, hip, spine), septic arthritis, nerve and/or arterial injuries, and cauda equina syndrome.

KEY POINTS: PEDIATRIC ORTHOPEDIC EMERGENCIES—NO DELAY!

1. Open fracture
2. Impending compartment syndrome
3. Dislocation of major joints
4. Septic arthritis
5. Nerve and/ or arterial injury

FOOT DISORDERS

27. Do infants and children need shoes?

Barefoot is the natural state of the foot. Humans evolved without shoes, and individuals who spend most of their lives unshod have stronger feet and fewer foot deformities than those who wear shoes. Before they begin walking, infants do not need foot coverings other than to keep their feet warm. Once the child begins to walk, shoes will offer protection from the cold and from sharp objects. The AAP recommends soft, light, flexible shoes for new walkers—not bulky, heavy so-called "orthopedic" shoes.

28. What is the most common congenital foot abnormality?

Metatarsus adductus. In patients with this condition, the forefoot is turned toward the midline as a result of adduction of the metatarsal bones at the tarsometatarsal joints. The hindfoot (heel) is normal (Fig. 15.5). Most cases are mild and flexible, with the foot easily straightened by passive stretching. A simple test to determine if the kidney-shaped curvature is within normal limits is to draw a line that bisects the heel. When extended, this line normally falls between the second and third toe space. If it falls more laterally, metatarsus adductus is present. In utero positioning is the suspected cause of the condition in many cases. It is seen more frequently in first-born children, presumably because primigravida mothers have stronger muscle tone in their uterine and abdominal walls.

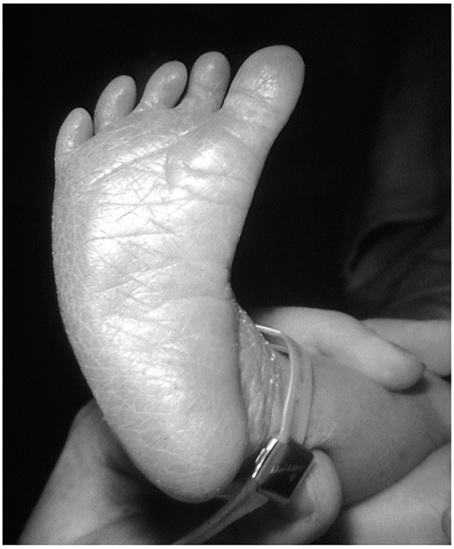

Fig. 15.5 Metatarsus adductus. (From Clark DA. *Atlas of Neonatology.* Philadelphia, PA: W.B. Saunders; 2000:224.)

29. How is metatarsus adductus treated?

If the foot can be passively abducted beyond neutral, the prognosis is excellent for a spontaneous correction without any therapeutic intervention. In those feet that are stiffer, a program of passive stretching is in order. The parents are taught to hold the heel in a neutral position and manually abduct the forefoot using their thumb placed over the cuboid as a fulcrum. This exaggerated position should be held for a few seconds and the stretching repeated 10 times each session. These sessions should occur with bathing and diaper changing. If this fails to improve the foot, bracing and/or casting can be of help.

30. An infant is born with the dorsum (top) of the foot touching the shin. Is this a worrisome condition?

This is a condition known as **calcaneovalgus foot**. Although it can appear dramatic and be upsetting to families, it is usually due to intrauterine positioning and molding and is a common normal physiologic variant. Overall, the foot is flexible, and both the heel and the forefoot can be corrected into a neutral position (Fig. 15.6). The condition typically resolves spontaneously. However, having parents passively stretch the foot may be beneficial (and makes the parents feel better and proactive). In rare, stiff cases of this condition, casting may be indicated to reposition the foot.

31. How is clubfoot distinguished from severe metatarsus adductus?

Clubfoot, or *talipes equinovarus,* is distinguished pathologically by a combination of forefoot and hindfoot abnormalities that results in a fixed (rigid) equinus and varus deformity of the hindfoot. *Metatarsus adductus* is often a component of clubfeet, but in isolated metatarsus adductus, the hindfoot (heel) is *normal*. If the ankle can be dorsiflexed to neutral or beyond, metatarsus is the most likely diagnosis.

32. How are clubfeet treated?

Most clubfeet respond well to **serial casting** using the Ponseti method. The casts should be applied soon after birth, and they are changed weekly. Over the course of three to eight casts, significant improvement in the shape of the foot

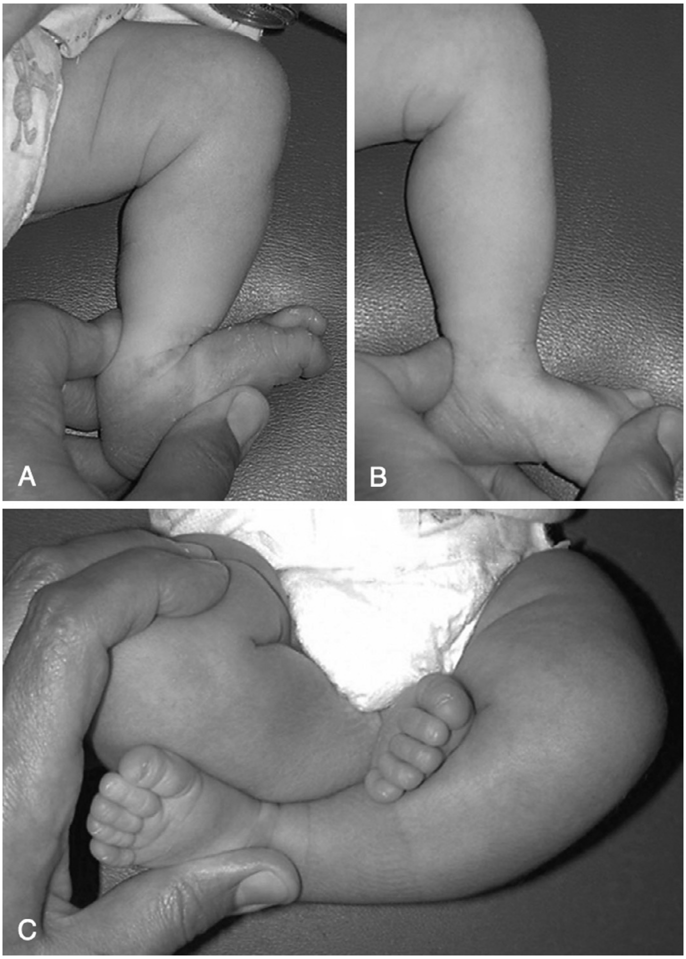

Fig. 15.6 Calcaneovalgus foot (A) that is passively correctable (B) and develops because of intrauterine positioning (C). (From Kliegman RM, St Geme JW, Blum NJ, et al, eds. *Nelson Textbook of Pediatrics.* 21st ed. Philadelphia, PA: Elsevier; 2020:3598.)

can be expected. About 80% of the feet that are corrected with casting will require an Achilles tenotomy to correct the equinus deformity. Those feet that are not adequately corrected with casting require a more extensive surgical release.

Smith PA, Kuo KN, Graf AN, et al. Long-term results of comprehensive clubfoot release versus the Ponseti method: which is better? *Clin Orthop Relat Res.* 2014;472(4):1281–1290.

33. What foot abnormality results in the appearance of a “Persian slipper” foot?

Also called *rocker bottom foot*, this abnormality is due to **congenital vertical talus**. Lateral radiographs reveal a vertically oriented talus with dislocation of the talonavicular joint. On examination, the forefoot is markedly dorsiflexed and the heel is rigid and points downward, giving the sole the characteristic convex or boat-shaped appearance. Serial casting and subsequent surgical reversion are the usual treatments. The syndrome most commonly associated with this deformity is trisomy 18.

34. What should be suspected when pes cavus is noted on examination?

Pes cavus, or high-arched feet (often associated with claw toes), can result from contractures or disturbed muscle balance (Fig. 15.7). A neurologic etiology should always be considered and looked for. The differential diagnosis includes a normal familial variant, Charcot-Marie-Tooth disease, spina bifida, cauda equina, peroneal muscle atrophy, Friedreich ataxia, Hurler syndrome, and polio.

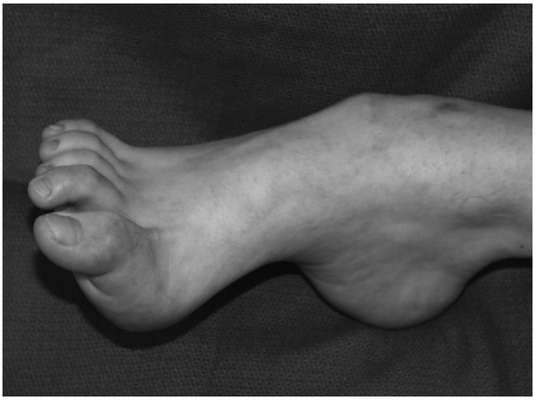

Fig. 15.7 Pes cavus. (From Myerson MS, Myerson CL. *Foot Ankle Clin.* 2019;24[2]:348.)

35. How common are flexible flat feet?

Flat feet (pes planus) refers to a condition where the medial longitudinal arch of the foot flattens out and may even touch the ground. Most flat feet are *flexible,* meaning that when the child is sitting or standing on tip toes, the arch gets bigger and looks normal. There are no functional consequences. Flexible flat feet are **very common**, affecting 15% to 20% of the population. No radiographic parameters define a flexible flat foot; it is felt to be a normal variant. Pathologic varieties of flat feet occur when there is rigidity without arch increase with toe raising, as well as limited tarsal/subtarsal joint range of motion *(rigid pes planus)* or where flat feet occur as part of a generalized ligamentous laxity syndrome (e.g., Ehlers-Danlos syndrome, Marfan syndrome).

Carr JB 2nd, Yang S, Lather LA. Pediatric pes planus: a state-of-the-art review. *Pediatrics.* 2016;137(3):e20151230.

36. Should children with flexible flat feet be given corrective shoes or orthotics?

Only in rare cases. Prospective studies have shown that corrective shoes or orthotic inserts do not change the natural history and are not necessary in young children with asymptomatic flexible flat feet. In many cases, the arch can spontaneously develop during the first 8 years of life, and even when they do not, many feet remain asymptomatic.

Carr JB 2nd, Yang S, Lather LA. Pediatric pes planus: a state-of-the-art review. *Pediatrics.* 2016;137(3):e20151230.

37. When should I worry about a child with flat feet?

Flat feet become concerning if they are **rigid** (the arch does not come back when weight is removed from the feet), **hypermobile** (the foot is completely collapsing, usually in kids with a connective tissue problem), **painful**, or **cause disability** (such as decreased walking or running endurance). If one or more of these conditions occurs, the child should be evaluated by a specialist for treatment, including physical therapy (to stretch the Achilles tendon and strengthen the foot and ankle muscles), orthotics, or in rare cases, surgery.

38. How does the cause of foot pain vary by age?

- *0 to 6 years:* Ill-fitting shoes, foreign body, occult fracture, osteomyelitis, inflammatory arthritis (such as juvenile rheumatoid arthritis), hypermobile flat foot
- *6 to 12 years:* Ill-fitting shoes, foreign body, accessory navicular bone, occult fracture, tarsal coalition (peroneal spastic flat foot), ingrown toenail, hypermobile flat foot
- *12 to 19 years:* Ill-fitting shoes, foreign body, ingrown toenail, pes cavus, hypermobile flat foot with tight Achilles tendon, ankle sprains, stress fracture

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Gross RH. Foot pain in children. *Pediatr Clin North Am.* 1986;33(6)1395–1409.

39. A 10-year-old boy with recurrent ankle sprains and painful flat feet should be evaluated for what possible diagnosis?

Tarsal coalition. Fusion of various tarsal bones via fibrous or bony bridges can result in a stiff foot that inverts with difficulty. When inversion of the foot is done during an examination, tenderness occurs on the lateral aspect of the foot, and peroneal tendons become very prominent. Thus this condition is also referred to as *peroneal spastic flat foot.* Unless the condition is very severe and warrants surgery, corrective shoes are usually adequate treatment. Other possible causes of a rigid flat foot include rheumatoid arthritis, septic arthritis, posttraumatic arthritis, neuromuscular conditions, and congenital vertical talus.

HIP DISORDERS

40. Why has developmental dysplasia of the hip (DDH) replaced congenital hip dislocation (CHD)?

The term DDH has replaced CHD to reflect the evolutionary nature of hip problems in infants during the first months of life. About 2.5 to 6.5 infants per 1000 live births develop problems, and a significant percentage of these are not present on neonatal screening examinations. Clearly, the overt pathologic process may not be present at birth, and periodic examination of the infant's hip is recommended at each routine well-baby examination until the age of 1 year.

DDH also refers to the entire spectrum of abnormalities involving the growing hip, ranging from dysplasia, to subluxation, to dislocation of the hip joint. Unlike CHD, DDH includes alterations in hip growth and stability in utero, during the newborn period, and during the period of infancy. DDH also refers to hip disorders associated with neurologic disorders (e.g., myelomeningocele), connective tissue disorders (e.g., Ehlers-Danlos syndrome), myopathic disorders (e.g., arthrogryposis multiplex congenital), and syndromic conditions (e.g., Larsen syndrome).

Bauchner H. Developmental dysplasia of the hip (DDH): an evolving science. *Arch Dis Child.* 2000;83(3):202.

41. What are the Ortolani and Barlow maneuvers?

The most reliable clinical methods of detection of hip pathology remain the Ortolani reduction and the Barlow provocative maneuvers. The infant should be lying quietly supine. Both examinations begin with the hips flexed to 90 degrees. To perform the *Ortolani maneuver,* the hip is abducted as the examiner's index finger gently pushes up on the greater trochanter. This is a reduction maneuver that allows a dislocated femoral head to "clunk" back into the acetabulum (Fig. 15.8A). The *Barlow maneuver* is performed by adducting the flexed hip and gently pushing the thigh posteriorly in an effort to dislocate the femoral head (Fig. 15.8B). After 3 to 6 months of age these tests are no longer useful because the hip becomes fixed in its dislocated position over time.

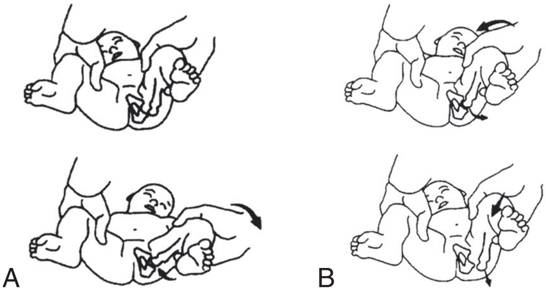

Fig. 15.8 (A) Ortolani maneuver. (B) Barlow maneuver. (From Staheli LT, ed. *Pediatric Orthopaedic Secrets.* Philadelphia, PA: Hanley & Belfus; 1998:166.)

KEY POINTS: THE FOUR FS OF INCREASED RISK FOR DEVELOPMENTAL DISLOCATION OF THE HIP

- First born
- Female
- Funny presentation (breech)
- Family history (positive for DDH)

42. What is the Galeazzi sign?

This test is performed by flexing both hips and knees together while evaluating the relative height of the knees. If one knee is significantly higher than the other, this can mean one of two things: the hip on the low side is dislocated or the femur on the low side is short. As opposed to the Ortolani and Barlow signs, the *Galeazzi sign* remains positive, and in fact usually becomes more obvious as the child gets older.

43. What is the significance of a "hip click" in a newborn?

A *hip click* is the high-pitched sensation felt at the very end of abduction when testing for DDH with the Barlow and Ortolani maneuvers; it occurs in ≤10% of newborns. Classically, it is differentiated from a hip "clunk," which is heard and felt as the hip goes in and out of joint. Although a debatable point, the hip click is felt to be **benign**. Its cause is unclear and may be the result of movement of the ligamentum teres between the femoral head and the acetabulum or tendons sliding over the greater or lesser trochanter. Worrisome features that might warrant evaluation (e.g., hip ultrasound, hip x-ray) include late onset of the click, associated orthopedic abnormalities, and other clinical features suggestive of developmental dysplasia (e.g., asymmetric skin folds/creases, unequal leg length).

McClure P, Podeszwa DA. Hip click in the neonate: should I be concerned? *Pediatr Ann.* 2016;45(4):e122–e127.
Witt C. Detecting developmental dysplasia of the hip. *Adv Neonatal Care.* 2003;3(2):65–75.

44. What is the most reliable physical finding for a dislocated hip in the older child?

Limited hip abduction. This is the result of shortening of the adductor muscles. Asymmetric abduction is a reliable finding in unilateral dislocation.

45. What other diagnostic signs are suggestive of a dislocated hip?

- **Waddling gait, hyperlordosis of lumbar spine:** This is seen in older patients with bilateral dislocations in whom most other findings may be normal given the symmetry (bilaterality) of the problem.
- **Unilateral toe walking** is consistent with a significant leg-length discrepancy, as can be seen in a unilateral hip dislocation.
- **Asymmetry of the thigh and gluteal folds:** However, these are often present in many normal (especially pudgy) infants, and it is an unreliable sign if all other tests are normal.

46. What radiographic studies are most valuable for diagnosing DDH during the newborn period?

In infants <6 months, the acetabulum and the proximal femur are predominantly cartilaginous and thus not visible on plain x-ray. In this age group, these structures are best visualized with **ultrasound**. In addition to morphologic information, ultrasound provides dynamic information about the stability of the hip joint.

Collins-Sawaragi YC, Jain K. How to use…hip examination and ultrasound in newborns. *Arch Dis Child Educ Pract Ed.* 2018;103(1):34–40.
Omeroğlu H. Use of ultrasonography in developmental dysplasia of the hip. *J Child Ortho.* 2014;8(2):105–113.

47. Should all infants be routinely screened by ultrasound for DDH?

The answer is not clear. Because physical examination is not completely reliable and the incidence of late-diagnosed DDH has not declined, some investigators have recommended routine ultrasonographic screening. Detractors argue that ultrasonography can lead to overdiagnosis and unnecessary treatment. At present, the issue remains controversial. A 2013 Cochrane review found insufficient evidence to recommend universal screening, which is more commonly done in Europe. In the United States, selective screening on the basis of risk factors and physical examination findings is more the norm.

Paton RW. Screening in developmental dysplasia of the hip (DDH). *Surgeon.* 2017;15(5):290–296.
Shorter D, Hong T, Osborn DA. Cochrane review: screening programmes for developmental dysplasia of the hip in newborn infants. *Evid Based Child Health.* 2013;8(1):11–54.
American Academy of Pediatrics. Clinical practice guideline: early detection of developmental dysplasia of the hip. *Pediatrics.* 2000;105(4 Pt 1):896–905.

48. Who is at a higher risk for DDH?

Dislocated, dislocatable, and subluxable hip problems occur in about 1% to 5% of infants. However, 70% of dislocated hips occur in **girls** and 20% occur in infants born in **breech position**. Other risk associations include the following:

- Congenital torticollis
- Skull or facial abnormalities
- First pregnancy
- Positive family history of dislocation
- Metatarsus adductus
- Calcaneovalgus foot deformities in infants <2500 g
- Amniotic fluid abnormalities (especially oligohydramnios)
- Prolonged rupture of membranes
- Large birth weight

MacEwen GD, Millet C. Congenital dislocation of the hip. *Pediatr Rev.* 1990;11(8):249–252.

49. How is DDH treated?

If the hip is dislocated, the first goal is to obtain a reduction and maintain that reduction to provide an optimal environment for femoral head and acetabular development. This is accomplished by keeping the legs abducted and the hips and knees flexed. The most commonly used devices are the Pavlik harness, the Frejka pillow, and the van Rosen splint. Double and triple diapers have *no role* in the treatment of DDH; they provide the parents with a false sense of security and do not provide reliabl[illegible]abilization or positioning. If the hip is merely shallow or loose and not

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[Ahmed Manfy] on TELEGRAM

frankly dislocated, the treatment is the same, but the harness or splint can come off once a day for an hour for bathing or play time.

Swarup I, Penny CL, Dodwell ER. Developmental dysplasias of the hip: an update on diagnosis and management from birth to 6 months. *Curr Opin Pediatr.* 2018;30(1):84–92.

Wenger DR, Bomar JD. Human hip dysplasia: evolution of current treatment concepts. *J Ortho Sci.* 2003;8(2):264–271.

50. What is the natural history of untreated DDH?

A child with a unilateral hip dislocation may have a leg-length discrepancy and painless (Trendelenburg) limp throughout childhood and young adulthood. If the hip is subluxated, osteoarthritis of the hip joint may develop at some point during the third through fifth decades of life. Hip fusion and total hip arthroplasty are surgical treatment options for the symptomatic hip in young adults. Children with bilateral DDH often have no leg-length inequality and no appreciable limp. They tend to walk with hyperextension of the lumbar spine (hyperlordosis) and have a waddling gait. As with patients with unilateral dislocations, these patients tend to develop early osteoarthritis. Total hip arthroplasty is the treatment of choice for adults with symptomatic bilateral DDH. Some recent studies suggest that a high percentage of newborns with DDH noted on ultrasound may spontaneously improve without treatment.

Sakkers R, Pollet V. The natural history of abnormal ultrasound findings in hips of infants under six months of age. *J Child Orthop.* 2018; 12(4):302–307.

Bialik V, Bialik GM, Blazer S, et al. Developmental dysplasia of the hip: a new approach to incidence. *Pediatrics.* 1999;103(1):93–99.

51. What is the significance of a positive Trendelenburg test?

When a normal individual stands on one leg, the ipsilateral hip abductors (primarily the gluteus medius) prevent the pelvis from tilting, and balance is maintained. Children >4 years can usually stand this way for at least 30 seconds. If the opposite side of the pelvis does tilt or the trunk lurches to maintain balance, this is a *positive Trendelenburg sign,* which usually indicates **hip abductor weakness** (Fig. 15.9). Patients with a Trendelenburg gait similarly will shift their torso away from the weak leg during the single-limb-stance phase of gait to compensate for the weak abductors.

52. What is the most common cause of a painful hip in a child <10 years old?

Transient synovitis (at one time called *toxic synovitis*) is a self-limited inflammatory condition that occurs before adolescence, has no known cause, and generally has a benign clinical outcome. Some theorize that it is an immune response to a viral illness, and many patients give a history of having a recent viral illness, but then again viral illnesses are very common in childhood. This disorder, although benign, can cause considerable anxiety among physicians and family members during its clinical course because it can mimic other, more sinister conditions such septic arthritis, osteomyelitis, LCP disorder, juvenile rheumatoid arthritis, and SCFE. It may occur anytime from the toddler age group to the late juvenile years, but the peak age of onset is between 3 and 6 years, and it is more common among boys. Acute transient synovitis remains a diagnosis of exclusion. Treatment consists of rest and calming of the synovitis with anti-inflammatory agents. Most patients experience complete resolution of their symptoms within 2 weeks of onset; the remainder may have symptoms of lesser severity for several weeks.

Ryan DD. Differentiating transient synovitis of the hip from more urgent conditions. *Pediatr Ann.* 2016;45(6):e209–e213.

Do TT. Transient synovitis as a cause of painful limps in children. *Curr Opin Pediatr.* 2000;12(1):48–51.

53. How can transient synovitis be differentiated from septic arthritis?

See Table 15.3.

54. What is LCP disease?

LCP disease (also called Perthes, Legg-Perthes, or Legg-Calvé-Perthes after the three physicians who independently described it in 1910) is a disorder of the femoral head of unknown etiology that is characterized by **ischemic necrosis**, **collapse**, and **subsequent repair** (Fig. 15.10). Children typically present with a limp that is often painless. Over time they often develop pain that localizes to the groin or is referred to the thigh or knee.

Divi SN, Bielski RJ. Legg-Calvé-Perthes disease. *Pediatr Ann.* 2016;45(4):e144–e149.

55. What are the pathologic stages of LCP disease?

LCP is a condition of aseptic necrosis of the femoral head involving children primarily between the ages of 4 and 10 years.

- **Incipient or synovitis stage**: Lasting 1 to 3 weeks, this first stage is characterized by an increase in hip-joint fluid and a swollen synovium associated with reduced hip range of motion.
- **Avascular necrosis**: Lasting 6 months to 1 year, the blood supply to part (or all) of the head of the femur is lost. That portion of the bone involved dies, but the contour of the femoral head remains unchanged.

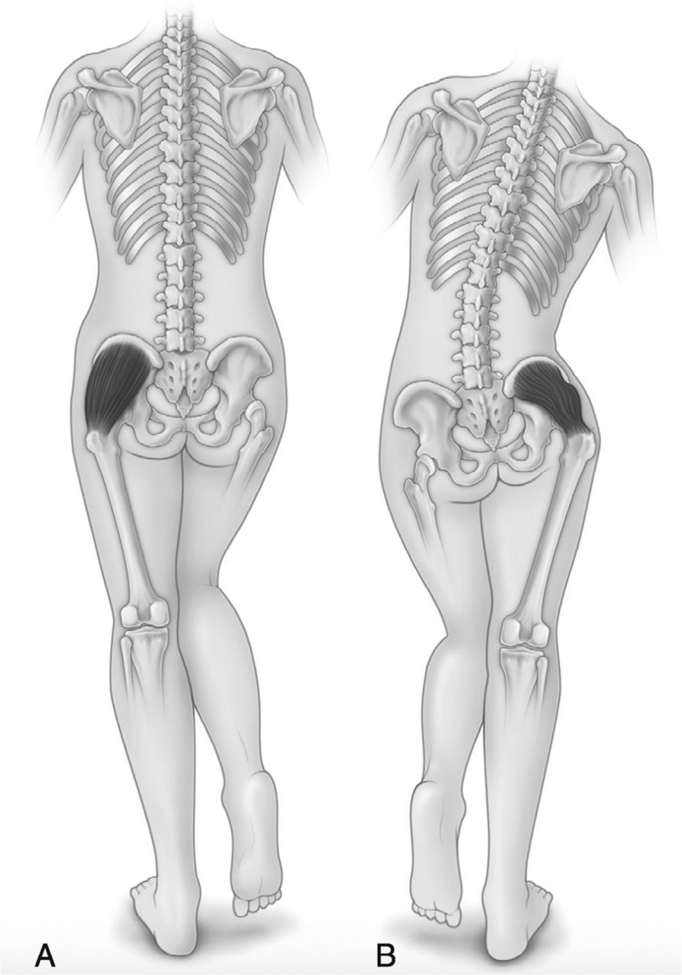

Fig. 15.9 Positive Trendelenburg test. (A) As the patient stands with the weight on the normal left hip, the pelvis is maintained in the horizontal position by contraction and tension of the normal left hip abductor muscles. (B) As the patient stands with the weight on the affected right hip, the pelvis on the opposite side drops and the torso shifts to the right as a result of weakness of the right hip abductor muscles. (From Herring JA, ed. *Tachdjian's Pediatric Orthopedics.* 5th ed. Philadelphia, PA: Elsevier Saunders; 2014:594.)

Table 15.3 Transient Synovitis Versus Septic Arthritis

	TRANSIENT SYNOVITIS	SEPTIC ARTHRITIS
History	Preceding upper respiratory infection ± low-grade fever Hip or referred knee pain Limp	Fever Usually large joint involvement (hip, ankle, knee, shoulder, elbow)
Physical	Refusal to bear weight Can delicately elicit range of motion in affected hip joint	Exquisite pain, swelling, warmth Marked resistance to mobility
Laboratory	ESR normal or mildly elevated Mild peripheral leukocytosis Negative blood culture Joint fluid cloudy Negative Gram stain	ESR markedly elevated Leukocytosis with left shift Often positive blood culture Joint fluid purulent Often positive Gram stain

ESR, Erythrocyte sedimentation rate.

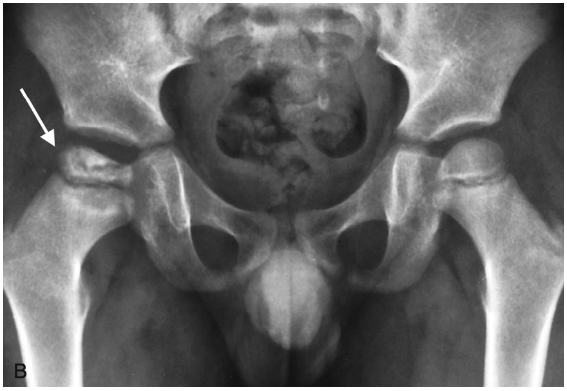

Fig. 15.10 Leg-Calvé-Perthes disease in a 7-year-old. Radiograph shows flattening with sclerosis and fragmentation of the right femoral capital epiphysis *(arrow)*; the left hip is normal. (From Zitelli BJ, McIntire SC, Norwalk AJ, eds. *Zitelli and Davis' Atlas of Pediatric Physical Diagnosis.* 7th ed. Philadelphia, PA: Elsevier; 2018:807.)

- **Fragmentation or regeneration and revascularization**: In the last and longest pathologic stage of LCP, which lasts 1 to 3 years, the blood supply returns and causes both the resorption of necrotic bone and the laying down of new immature bone. As the dead bone is removed, the integrity of the head is weakened and it collapses. Permanent hip deformity can occur during this last stage.

It is important to note that plain radiographs may lag behind the progression of the disorder by as much as 3 to 6 months. Radionuclide bone scans and MRI are much better, because ischemia and avascular necrosis can be detected much earlier.

56. What are the most important prognostic factors for children with LCP disease?

The **age of the child at diagnosis** and the **amount of epiphyseal involvement** are most helpful in guiding prognosis. Children <6 years old tend to have a more favorable prognosis, and those with less epiphyseal involvement also tend to have a better prognosis. Epiphyseal involvement has been classified by Salter into type A (those with <50% epiphyseal involvement) and type B (those with >50% head involvement).

57. Which conditions are associated with coxa vara?

Coxa vara is a condition of a decreased femur shaft-neck angle to <120 degrees. Normal angles range from 150 degrees in infants to 120 degrees in adults. The result is a shortening of the leg and, if unilateral, a limp. The three most common associations are **developmental coxa vara**, **avascular necrosis of the femoral head**, and **cleidocranial dysostosis**.

58. What condition does the child in Fig. 15.11 have?

This is **femoral anteversion** (or medial femoral torsion), which is a common cause of in-toeing in younger children. The child demonstrates the reverse tailor, or "W," position, which is a sign of the internally rotated hip.

59. How is the extent of femoral anteversion measured?

With the child lying prone and knees flexed at 90 degrees, the hip normally cannot be rotated internally (i.e., feet pushed outward) more than 60 degrees (angle A in Fig. 15.12A). In addition, external rotation (angle B in Fig. 15.12B) should exceed 20 degrees. A normal child averages approximately 35 degrees. Motion outside these ranges indicate that the cause of in-toeing is likely the result of physiologic femoral anteversion (or, less commonly, hip capsular contractions as are seen in patients with cerebral palsy).

60. Is sitting in the "W" position harmful?

In a word, **no**. Although there is great confusion about this among many physicians and patients alike, there is absolutely no evidence that sitting in the "W" position has a harmful effect on the development of the hip and knee. Similarly, use of special orthopedic shoes or the infamous boots and bars that hold the feet turned in have no effect on the bony alignment of the proximal femur.

61. Is there ever an indication to treat femoral anteversion?

The neurologically normal child almost never requires treatment for anteversion. Although they may walk with their feet turned in, especially early in life, this tends to improve as they age and improve in strength, coordination, and balance. An exception is the child with so-called *miserable malalignment syndrome* who has severe femoral anteversion along with external tibial torsion. This child walks with their feet straight ahead (the tendency to in-toe is counter balanced by the external rotation of the foot through the tibia), but the knees are pointed in, and this places severe stress across the patellofemoral joint. Significant knee pain and disability follow. The treatment is quite

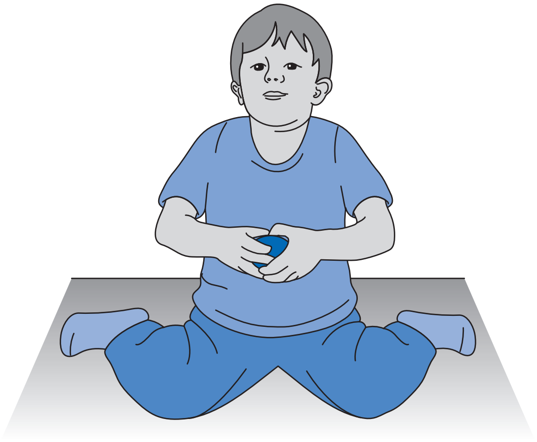

Fig. 15.11 Reverse tailor position or "W" position.

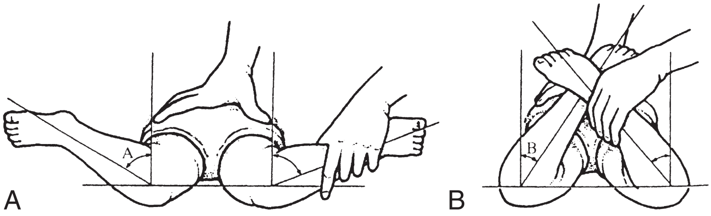

Fig. 15.12 Measurement of femoral anteversion including angle A in internal rotation (A) and angle B in external rotation (B). (From Dormans JP. Orthopaedic management of children with cerebral palsy. *Pediatr Clin North Am;* 1993:40:650.)

significant, involving osteotomies of the femurs and tibias, but most patients respond well with much improved knee mechanics and decreased pain.

62. What are the symptoms of children and adolescents who develop SCFE?

SCFE involves progressive displacement with external rotation of the femur on the epiphyseal growth plate. It is the most common hip disorder in adolescents. The patient has **intermittent or constant hip, thigh, or knee pain** that has often been present for weeks or months. A **limp**, a **lack of internal rotation**, and an **inability to flex the hip** without also abducting may be noted. It is important to realize that any patient with knee pain may have underlying hip pathology.

Uvodich M, Schwend R, Stevanovic O, et al. Patterns of pain in adolescents with slipped capital femoral epiphysis. *J Pediatr.* 2019;206:184–189.e1.

63. What systemic conditions are associated with SCFE?

Children with SCFE tend to have *delayed skeletal maturation* and *obesity* and usually present between the ages of 8 and 14 years. It is more common in boys and in black children. Systemic conditions associated with SCFE include **hypothyroidism**, **panhypopituitarism**, **hypogonadism**, **rickets**, and **irradiation**.

64. What does FAI stand for?

Femoral acetabular impingement syndrome. This is a relatively recently recognized entity thought to be a significant cause of hip pain and disability in adolescents and young adults. Similar to the way the rotator cuff of the shoulder can be damaged when impinged between the humeral head and acromion, the labrum of the hip (a structure analogous to the meniscus in the knee) can be torn when pinched between the acetabulum and femoral head or neck.

Pathy R, Sink EL. Femoroacetabular impingement in children and adolescents. *Curr Opin Pediatr.* 2016;28(1):68–78.

65. What new treatments are available for hip pathology, including DDH, FAI, and SCFE?

Over the last decade **hip arthroscopy** has come into much more frequent use to diagnose and treat hip pain due to labral tears, as well as to recontour the bony aspects of the hip joint when some types of dysplasia exist. Even more recently, some hip centers around the country have been describing their experience with repairing hip pathology through **surgical dislocation of the hip**. This technique has been eschewed in the past because of concerns of osteonecrosis of the femoral head as a complication. However, newer techniques in the right hands have shown extremely low rates of osteonecrosis, and this procedure allows more direct and effective treatment of many hip problems, including unstable SCFE and FAI.

Guindani N, Eberhardt O, Wirth T, et al. Surgical dislocation for pediatric and adolescent hip deformity: clinical and radiological results at 3 years follow-up. *Arch Orthop Trauma Surg.* 2017;137(4):471–479.

Ricciardi BF, Sink EL. Surgical hip dislocation: techniques for success. *J Pediatr Orthop.* 2014;34(Suppl 1):S25–S31.

INFECTIOUS DISEASES

66. What percentage of septic arthritis is "culture negative"?

Several studies have established that **30% to 60%** of patients with clinically apparent septic arthritis have negative cultures of joint fluid. Reasons (both postulated and confirmed) for this observation include the fastidious nature of some less common etiologies of infectious arthritis (e.g., *Kingella kingae*), the loss of viability of some organisms on transport to the laboratory (e.g., *Neisseria* species), and perhaps a substance or cell population in the aspirate fluid that is bacteriostatic during in vitro culture conditions. Prompt processing of specimens and the use of several culture techniques (e.g., solid media plus liquid-culture systems, such as those used for blood cultures) can increase the yield of joint fluid cultures

67. Where does acute hematogenous osteomyelitis most commonly localize in children?

Hematogenous osteomyelitis refers to an infection of bone that begins as a seeding of bacteria transported via the bloodstream. This contrasts with *direct inoculation* (e.g., trauma, surgery) or *contiguous spreading* from a nearby infection (e.g., cellulitis). Approximately two-thirds of all cases of hematogenous osteomyelitis involve the **femur**, **tibia**, or **fibula**.

68. What is the most common cause of osteomyelitis in children?

Staphylococcus aureus, which is the cause in two-thirds of cases in which an organism is isolated. Although most *S. aureus* is methicillin-sensitive (MSSA), the percentages of methicillin-resistant *S. aureus* (MRSA) have increased significantly.

Sarkissian EJ, Gans I, Gunderson MA, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* musculoskeletal infections: emerging trends over the past decade. *J Pediatr Orthop.* 2016;36(3):323–327.

Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. *J Bone Joint Surg Br.* 2012;94(5):584–595.

69. How helpful is a screening white blood cell (WBC) count for the diagnosis of osteomyelitis?

Not very. In two-thirds of patients, the total WBC count is normal (although in one-half of these, the differential is shifted to the left). In the other one-third, the WBC count is elevated, usually with a left shift. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are more sensitive. Ninety-five percent of cases will have an ESR $>$20 mm/hr with an average rate of 70 mm/hr. Likewise, 95% of cases will have an elevated CRP of $>$10 to 20 mg/dL. Although elevations of ESR and CRP have a high sensitivity, they have a very low specificity for osteomyelitis, as they are increased in multiple inflammatory conditions.

Saawedra-Lozano J, Falup-Pecurariu O, Faust SN, et al. Bone and joint infections. *Pediatr Infect Dis J.* 2017;36(8):788–799.

70. How often are blood cultures positive in patients with osteomyelitis?

Fifty percent of the time or less. Because this rate is relatively low, direct bone aspiration should be strongly considered, especially in the setting of an abscess. Aspiration raises the yield to 70% to 80% and can facilitate antibiotic therapy.

71. As osteomyelitis progresses, how soon do x-ray changes occur?

- *3 to 4 days:* Deep muscle plane shifted away from periosteal surface
- *4 to 10 days:* Blurring of deep-tissue muscle planes
- *10 to 15 days:* Changes in bone occur (e.g., osseous lucencies, punched-out lytic lesions, periosteal elevation)

72. What is the best way to confirm the diagnosis of osteomyelitis?

Bone infections in children are typically accompanied by fever, local pain, and decreased use of the affected body part (e.g., limp or failure to bear weight). Although point tenderness is often elicited, plain radiographs may appear normal during the first 7 to 10 days of infection, until a sufficient portion of cortex is damaged and the periosteal reaction becomes apparent. Early during the course of infection, other imaging studies (bone scintigraphy or MRI) or direct aspiration with Gram stain and culture can be of use for confirming the diagnosis. MRI is especially valuable because it can simultaneously assess the osseous, articular, and muscular structures without ionizing radiation exposure (Fig. 15.13).

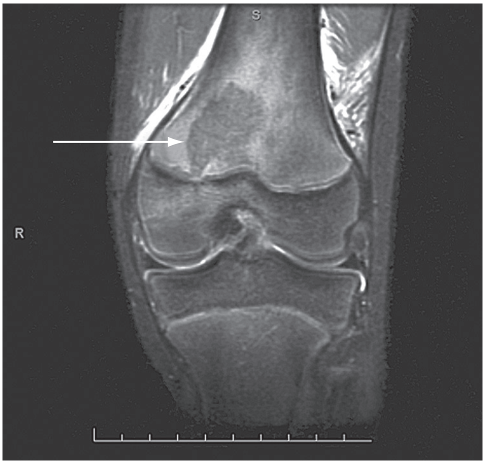

Fig. 15.13 MRI image of the distal femur showing metaphyseal lesion *(arrow)* and overlying inflammatory edema of muscles, consistent with osteomyelitis. (From Bergelson JM, Shah SS, Zaoutis TE. *Pediatric Infectious Diseases: The Requisites in Pediatrics.* Philadelphia, PA: Elsevier Mosby; 2008:239.)

73. How long should antibiotics be continued in patients with osteomyelitis and septic arthritis?

The precise answer is unclear, but infections caused by *S. aureus* or enteric gram-negative bacteria must be treated for longer periods than those caused by *Haemophilus influenzae, Neisseria meningitidis,* or *Streptococcus pneumoniae*. A minimum of 4 to 6 weeks is likely necessary for the former group, and 2 to 3 weeks are needed for the latter. If diagnosis has been delayed, if initial clinical response is poor, or if the ESR remains elevated, longer durations may be needed. Although initial management involves intravenous (IV) antibiotics, patients with clear clinical improvement (e.g., afebrile ≥48 hours, normalization of inflammatory markers, decreased localized symptoms) are commonly switched to oral antibiotics to complete the duration of therapy.

Keren R, Shah SS, Srivastava R, et al. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr.* 2015;169(2):120–128.

74. When is open surgical drainage indicated in cases of osteomyelitis?

- Abscess formation in the bone, subperiosteum, or adjacent soft tissue
- Bacteremia persisting >48 to 72 hours after the initiation of antibiotic treatment
- Continued clinical symptoms (e.g., fever, pain, swelling) >72 hours of therapy
- Development of a sinus tract
- Presence of a sequestrum (i.e., detached piece of necrotic bone)

Darville T, Jacobs RF. Management of acute hematogenous osteomyelitis in children. *Ped Infect Dis J.* 2004;23(3):255–257.

KEY POINTS: OSTEOMYELITIS

1. The most common causative organism in healthy children is *S. aureus*.
2. In children (unlike adults), spread of bacteria to bone is hematogenous rather than by local trauma.
3. In children with a puncture wound through a sneaker and osteomyelitis, think of *Pseudomonas aeruginosa*; however, the most common organism is still *S. aureus*.
4. Because of intravascular sludging and infarction, patients with sickle cell disease are at increased risk, especially for *Salmonella* infections.
5. Bone changes on x-ray may not occur for 10 to 15 days after onset of infection. MRI is more sensitive early in the course of infection.

75. Why are treatment failures more common in osteomyelitis than in septic arthritis?

- Antibiotic concentrations are much greater in joint fluid than in inflamed bone. Concentrations in joint fluid may actually exceed peak serum concentrations, whereas those in bone may be significantly less than serum concentrations.
- Devitalized bone may serve as an ongoing nidus for infection, and it has no blood flow to bring in antibiotics.
- Diagnosis of osteomyelitis is more likely to be delayed than that of septic arthritis.

76. How do the features of osteomyelitis in the neonate differ from those seen in the older child and adult?

- Multiple foci of infection are frequently seen.
- Septic arthritis is a frequent association, probably reflecting the spread of infection via blood vessels penetrating the epiphyseal plates.
- The pathogens causing neonatal osteomyelitis are the same as those responsible for sepsis neonatorum.

77. How is the diagnosis of discitis established?

Discitis, which is the infection and/or inflammation of the intervertebral disc, most commonly occurs in children between the ages of 4 and 10 years. The etiology is often unclear, but a bacterial cause (particularly *S. aureus*) is identified by blood cultures in about 50% of cases. The diagnosis can be difficult because the symptoms can be vague and vary greatly. Symptoms include generalized back pain with or without localized tenderness, limp, refusal to stand or walk, back stiffness with loss of lumbar lordosis, abdominal pain, and unexplained low-grade fever.

As with osteomyelitis, a helpful laboratory test is an elevated CRP or ESR. WBC counts may often be normal, and early x-rays (<2 to 4 weeks of symptoms) may not show changes. Technetium-99 bone scans will demonstrate abnormalities early during the course of illness. MRI studies can help distinguish between discitis and vertebral osteomyelitis. Treatment consists of 3 to 6 weeks of antistaphylococcal antibiotics, with variable amounts of immobilization and bracing to control symptoms. Persistent or atypical cases may require biopsy to identify the etiology, but this is unusual.

Early SD, Kay RM, Tolo VT. Childhood diskitis. *J Am Acad Orthop Surg.* 2003;11(6):413–420.

78. What is an important variable that influences mortality in necrotizing fasciitis?

Time to surgical débridement. *Necrotizing fasciitis* is a deep soft-tissue infection that can rapidly cause necrosis of fascial planes and surrounding tissue. The infection commonly follows trauma, but even minor insults (e.g., scrape, insect bite) can be implicated. High clinical suspicion is key to early diagnosis. *Pain out of proportion to clinical findings* is an important clue to the diagnosis. Aggressive and early surgical débridement, coupled with antibiotic therapy, constitute the primary treatment for this disease, which has been called *flesh-eating bacteria syndrome* in the popular media.

Zundel S, Lemaréchal A, Kaiser P, Szavay P. Diagnosis and treatment of pediatric necrotizing fasciitis: a systematic review of the literature. *Eur J Pediatr Surg.* 2017;27(2):127–137.

79. What is the role of bone scintigraphy in children with obscure skeletal pain?

In the child with vague symptoms who is not clearly localizing to a specific anatomic location, a bone scan can help localize an abnormality in the bones, joints, or soft tissues. Once localized, the region can be further evaluated with three-dimensional imaging such as MRI or CT scan, if indicated. Bone scans are very sensitive but not very specific. Therefore a negative bone scan makes the likelihood of a serious problem like infection or tumor unlikely, which can be comforting to the physician and family. A bone scan should be considered only after a careful history and physical examination have been performed and plain x-rays of the abnormal area are obtained. The scan is most useful for establishing or ruling out occult infection or bone tumor.

Palestro CJ. Radionuclide imaging of musculoskeletal infection: a review. *J Nucl Med.* 2016;57(9):1406–1412.

80. What are the phases of a bone scan?

There are three phases in a bone scan defined by the time elapsed since injection of the radionuclide dye.

- **Phase I**—*Angiographic phase*: During the first few seconds, the dye passes through the large blood vessels and provides early assessment of regional vascularity and perfusion.
- **Phase II**—*Blood pool phase*: Usually obtained during the first minutes after an injection, this phase highlights the movement of the dye into the extracellular spaces of soft tissue and bone.
- **Phase III**—*Delayed phase*: By 1.5 to 3 hours after injection, the dye localizes in the bone with minimal soft-tissue imaging.

The three-phase process is used to differentiate soft tissue from bony abnormalities. At times a **phase IV** study may be done by rescanning for the same dye at 24 hours, which further minimizes soft-tissue background activity.

KNEE, TIBIA, AND ANKLE DISORDERS

81. What is the difference between valgus and varus deformities?

Some things seem to be destined to be learned, forgotten, and relearned many times as a rite of passage: the Krebs cycle is one, and this is another. The terms refer to angular deformities of the musculoskeletal system. If the distal part (part farther from the trunk) of the deformity points toward the midline, the term is *varus*. If the distal part points away from the midline, it is *valgus*. For example, in patients with knock knees, the lower portion of the deformity points away, so the term is genu valgum.

82. Are children normally knock-kneed or bowlegged?

The answer is **yes**. *Both can be normal depending on the age of the child.* Most children at birth are bowlegged (genu varum) up to 20 degrees, but this tendency progressively diminishes until about 24 months, when the trend toward knock knees (genu valgum) begins. Knock knees are most noticeable at around the age of 3 years (up to 15 degrees) and then begin to diminish. By 8 years of age, most children are—and will remain—in neutral alignment, meaning that with their knees extended their knees and ankles both touch (Fig. 15.14).

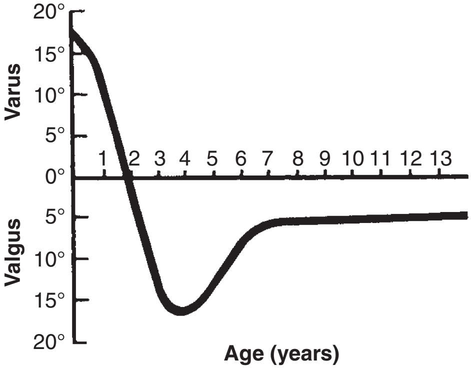

Fig. 15.14 Development of the tibiofemoral angle during growth. (From Bruce RW Jr. Torsional and angular deformities. *Pediatr Clin North Am.* 1996:43(4):875.)

83. Which bowlegged infants or toddlers require evaluation?

Radiographs should be considered if bowleggedness demonstrates any of the following features:

- Present >24 months (the age when most children start to develop physiologic genu valgum)
- Progressive varus develops >age 1 year as the infant begins to bear weight and walk
- Unilateral deformity
- Visually >20 degrees of varus angulation across the knee

It is important to remember that clinical or radiographic evaluation of alignment in the legs requires the knees to be pointed straight ahead. If the knees are pointed in or out, flexion at the knee can be easily mistaken for bowing of the legs.

84. What are the causes of pathologic genu varum (bowleggedness) or genu valgus (knock knees)?

Genu varum

- Physiologic bow legs
- Infantile tibia vara (Blount disease)
- Hypophosphatemic rickets
- Metaphyseal chondrodysplasia
- Focal fibrocartilaginous dysplasia

Genu valgum

- Hypophosphatemic rickets
- Previous metaphyseal fracture of the proximal tibia (Cozen fracture)
- Multiple epiphyseal dysplasia
- Pseudoachondroplasia

Sass P, Hassan G. Lower extremity abnormalities in children. *Am Fam Physician.* 2003;68(3):461–468.

85. Which children are more likely to develop Blount disease?

Tibia vara, or *Blount disease,* is a medial angulation of the tibia in the proximal metaphyseal region as a result of a growth disturbance in the medial aspect of the proximal tibial epiphysis. In the *infantile type,* the child is usually an obese early walker, and he or she develops pronounced bowlegs during the first year of life. Black females are particularly at risk for severe deformity. In the *adolescent variety,* the onset occurs during late childhood or early adolescence, and the deformity is usually unilateral and milder. Although bracing may be effective in some infantile cases diagnosed in the first 2 years of life, correction of severe deformity usually requires surgical intervention.

Sabharwal S. Blount disease: an update. *Orthop Clin North Am.* 2015;46(1):37–47.

86. How does tibial torsion change with age?

Tibial torsion, the most common cause of in-toeing in children between the ages of 1 and 3 years, **gradually rotates externally with age**. For excessive internal rotation, bracing was used extensively in the past, but its efficacy is questionable because the natural history of the condition is self-resolution. Measurement is done by measuring the angle made by the long axis of the foot and the thigh when the knee is flexed 90 degrees.

87. How effective is the Denis Browne splint for the treatment of tibial torsion?

Not at all. The splint consists of a metal bar connected to shoes and holds the feet in varying degrees of external rotation. The splint was used frequently in the past for children with tibial torsion. However, there is absolutely no scientific evidence that this device alters the natural history of tibial torsion, and there is no role for its use.

88. Why are ligament tears seen less commonly than fractures in children compared with adults?

In children, ligaments tend to be stronger than the cartilaginous growth plates. It is the growth plate that usually fails (i.e., fractures) before the ligament tears.

89. How are ankle sprains graded?

Between 80% and 90% of ankle sprains are the result of excessive inversion and/or plantar flexion resulting in injury to the lateral ligaments (anterior talofibular and calcaneofibular).

- **Grade 1** ankle sprain is a mild, partial tear of the ankle ligament and results in no instability.
- **Grade 2** sprain is a high-grade partial tear. Clinically differentiating between a grade 1 and 2 can be challenging, but usually does not change treatment.
- **Grade 3** sprain is a complete tear of the ligament. This will result in some instability of the ankle, which can be detected with the ankle drawer test. This test is performed by immobilizing the lower tibia with one hand as the other hand grasps the heel and pulls the foot forward. There is always some motion (test the unaffected side to get an idea of what is normal for that patient), but with a complete tear there is marked laxity with a poor endpoint.

90. Which ankle sprains should be evaluated with an x-ray?

More than 5,000,000 radiographs are estimated to be taken annually in children and adults for ankle injuries, yet there are no widely accepted guidelines. One set of guidelines (the Ottawa Ankle Rules) suggests obtaining an x-ray if there is malleolar pain and one or both of the following conditions is present: (1) the inability to bear weight for four steps immediately after the injury and during office or emergency room evaluation and/or (2) bone tenderness at the posterior edge or tip of either malleolus. When these simple criteria were used in studies involving children and adults, no fractures were missed and unnecessary x-rays were reduced by 25%.

Barelds I, Krijnen WP, van de Leur JP, et al. Diagnostic accuracy of clinical decision rules to exclude fractures in acute ankle injuries: systematic review and meta-analysis. *J Emerg Med.* 2017;53(3):353–368.

Dowling S, Spooner CH, Liang Y, et al. Accuracy of Ottawa Ankle Rules to exclude fractures of the ankle and midfoot in children: a meta-analysis. *Acad Emerg Med.* 2009;16(4):277–287.

91. Should ankle sprains be casted?

No. If inversion ankle sprains are not complicated by a fracture or peroneal tendon dislocation, casting is not warranted. Casting has no benefit over early immobilization with a functional brace, and in fact, complete immobilization may actually delay rehabilitation.

92. After an acute injury, a 15-year-old boy has immediate swelling of his knee. What is the fluid, and how did it get there?

Fluid in the setting of injury almost always has to be **blood**, so in this setting there is an acute hemarthrosis. The presence of a hemarthrosis tells you that a structure was torn or fractured. The most common causes in the knee are:

- Rupture of the anterior or posterior cruciate ligaments
- Peripheral meniscal tears
- Intra-articular fracture
- Tear in the joint capsule

93. A 5-year-old boy with a painless swelling in the back of his knee has what likely condition?

Popliteal cyst. Also called *Baker cysts,* these occur more frequently in boys, are usually found on the medial side of the fossa, and are painless. In children, the cysts are rarely associated with intra-articular pathology. The mass should transilluminate on physical examination, confirming the fluid-filled nature of the lesion. The natural history is for the cyst to disappear spontaneously after 6 to 24 months. Surgery is not required except in extraordinary circumstances, such as unremitting pain. Atypical findings (e.g., tenderness, firmness, history of rapid enlargement, pain) are justification for further diagnostic evaluation.

Herman AM, Marzo JM. Popliteal cysts: a current review. *Orthopedics.* 2014;37(8):678–684.

94. What predisposes a child or teenager to recurrent dislocation of the patella?

- **Problems with alignment**: Genu valgum, laterally displaced tibial tubercle, patella alta
- **Developmental problems**: Hypoplasia of the lateral femoral condyle, vastus medialis (VMO) insufficiency, abnormal attachment of the iliotibial tract
- **Generalized ligamentous laxity**: Down syndrome, Ehlers-Danlos syndrome, Marfan syndrome, Turner syndrome

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Seitlinger G, Ladenhauf HN, Wierer G. What is the chance that a patella dislocation will happen a second time: update on the natural history of a first time patella dislocation in the adolescent. *Curr Opin Pediatr.* 2018;30(1):65–70.

95. How does patellofemoral stress syndrome occur?

This major cause of chronic knee pain in teenagers results from **malalignment of the extensor mechanism of the knee**. It is most commonly seen as an “overuse” entity in sports that involve running and full-knee flexion (e.g., track, soccer). It has been inappropriately called *chondromalacia patella,* which is a specific pathologic diagnosis of an abnormal articular surface that occurs in a minority of these patients. The patella serves as the fulcrum on which the quadriceps extends the knee. The multiple muscle bellies of the quadriceps may act asymmetrically, causing greater stress on the lateral aspect of the patella. This is particularly a problem for individuals with problems placing them at risk for patellar symptoms, including femoral anteversion, external tibial torsion, high (alta) patella, abnormally developed quadriceps, excessive flattening of the trochlear groove, or an increased Q angle. Treatment consists of ice, rest, NSAIDs, quadriceps strengthening, hamstring stretching, and possibly patellar-stabilizing braces.

96. What is the Q (quadriceps) angle?

This angle describes the **lines of force acting on the patella**. The angle is formed by the intersection of a line drawn from the anterosuperior iliac spine to the patella and a line from the patella to the tibial tubercle (Fig. 15.15). For teenage males, the average Q angle is 14 degrees, and for females, it is 17 degrees. Angles of $>$20 degrees create a bowstringing effect, which places a lateral stress on the patella and predisposes individuals (particularly runners) to chronic knee pain.

97. What is *a common* significant mistake made during the evaluation of knee pain?

Failure to evaluate the hip as a source of the pain. Hip pathology frequently masquerades as knee or distal thigh pain (e.g., LCP disease, SCFE).

SPINAL DISORDERS

98. What signs and symptoms suggest a serious cause of back pain in a child that warrants further evaluation?

Back pain in children is a common symptom, with estimates of prevalence of 1% at age 7 years, 6% at age 10 years, and 18% at ages 14 to 16 years. Although most back pain is musculoskeletal and self-limiting, features that are concerning for a more serious cause include:

- *Symptoms:* age $<$4 years; pain interfering with daily activities in school, play, or athletics; pain lasting longer than 4 weeks; night pain; pain radiating down the leg; fever or other systemic symptoms; limp or altered gait; bowel or bladder habit changes
- *Signs:* postural changes; clawing of the toes, gait changes, other neurologic abnormalities; reproducible point tenderness; pain with hyperextension of the back

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MacDonald J, Stuart E, Rodenberg R. Musculoskeletal low back pain in school-aged children: a review. *JAMA Pediatr.* 2017; 171(3):280–287.

Davis PJ, Williams HJ. The investigation and management of back pain in children. *Arch Dis Child Educ Pract Ed.* 2008;93(3):73–83.

99. What is the differential diagnosis of back pain in children?

- **Infectious:** discitis, vertebral osteomyelitis, vertebral tuberculosis
- **Developmental:** spondylolysis, spondylolisthesis, Scheuermann kyphosis, scoliosis
- **Traumatic:** herniated disc, muscle strain, fractures, vertebral apophyseal fracture

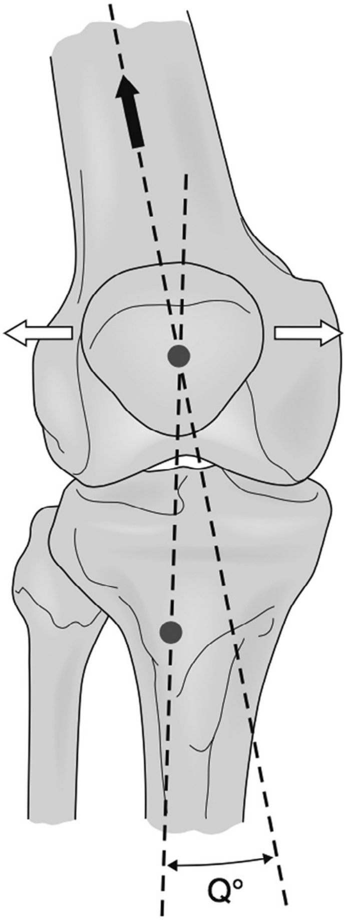

Fig. 15.15 Measurement of Q angle. Quadriceps muscle contraction *(superior arrow)* will cause medial *(right arrow)* or lateral *(left arrow)* forces based on Q angle. (From Frontera WR, Silver JK, Rizzo D, Jr, eds. *Essentials of Physical Medicine and Rehabilitation.* 4th ed. Philadelphia, PA: Elsevier; 2019:415.)

- **Inflammatory:** juvenile idiopathic arthritis, ankylosing spondylitis
- **Neoplastic:** eosinophilic granuloma, osteoid osteoma or osteoblastoma, aneurysmal bone cyst, leukemia, lymphoma, Ewing sarcoma, osteosarcoma
- **Visceral:** urinary tract infection, hydronephrosis, ovarian cysts, inflammatory bowel disease

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MacDonald J, Stuart E, Rodenberg R. Musculoskeletal low back pain in school-aged children: a review. *JAMA Pediatr.* 2017; 171(3):280–287.

100. Do school backpacks contribute to back pain?

Probably, but this is controversial. Some experts suggest that the limits of maximum loads lifted by children should be 10% to 15% of body weight. In some studies, more than one-third of students carried more than 30% of their body weight at least once during the school week. MRI studies have demonstrated significant disc compression and lumbar asymmetry as backpack loads increased from 10% to 30% of body weight. With an apparent increasing incidence of back pain in children and adolescents (particularly those with open physes), there is concern that a bulging backpack may be one contributing cause.

Dockrell S, Simms C, Blake C. Schoolbag weight limit: can it be defined? *J Sch Health.* 2013;83(5):368–377.
Neuschwander TD, Cutrone J, Macias BR, et al. The effect of backpacks on the lumbar spine in children: a standing magnetic resonance imaging study. *Spine (Phila Pa 1976).* 2010;35:1:83–88.

KEY POINTS: BACK PAIN

1. Back pain is common in children.
2. The intense dancer or sports athlete with low back pain, especially pain in extension, needs to be evaluated for a stress fracture (spondylolysis).
3. Back pain that is traumatic, has associated neurologic findings, or lasts >4 weeks and limits participation in activities the child enjoys should be taken seriously and evaluated by a specialist.

101. What are the different forms of scoliosis?

Scoliosis is a *lateral curvature* of the spine (i.e., coronal plane deformity) that has several causes.

- **Idiopathic scoliosis:** This is the most common form that arises in otherwise normal children for reasons that are not fully understood, but there is an underlying genetic cause. Idiopathic scoliosis is subdivided according to age at which the disease is diagnosed, typically dividing them into two groups: early-onset (≤9 years of age) and adolescent (>10 years).
- **Congenital scoliosis** occurs when there is a problem with the way the vertebrae form during embryogenesis. This form of scoliosis may be associated with anomalies of the cardiac and renal systems, which are developing at the same time.
- **Neurogenic scoliosis** is associated with a variety of spastic and paralytic neuromuscular diseases such as cerebral palsy, muscular dystrophy, and myelomeningocele.
- **Miscellaneous:** Typically syndromic, these causes of scoliosis can be associated with connective tissue disorders like Marfan and Ehlers-Danlos syndromes. Scoliosis is also seen at increased rates in children who have undergone major abdominal or thoracic surgery in infancy (such as open heart surgery or congenital diaphragmatic hernia repair).

Konieczny MR, Senyurt H, Krauspe R. Epidemiology of adolescent idiopathic scoliosis. *J Child Orthop.* 2013;7(1):3–9.
Ahn UM, Ahn NU, Nallamshetty L, et al. The etiology of adolescent idiopathic scoliosis. *Am J Ortho.* 2002;31(7):387–395.
National Scoliosis Foundation. www.scoliosis.org. Accessed July 27, 2019.

102. How is screening for spinal deformity performed?

The child should be undressed or dressed only in underwear with a gown open at the back. The child is asked to bend forward while standing, and the contour of the back is examined from behind and the side. This examination is then repeated with the child sitting. The following signs can suggest scoliosis:

- Shoulder or scapular asymmetry.
- Asymmetry of paraspinal muscles or rib cage (the so-called *rib hump*) in the thoracic spine noted on forward bending.
- Sagittal plane deformity, such as increased kyphosis, when viewed from the side.
- Waist-crease asymmetry that does not disappear when sitting (some waist-crease asymmetries are the result of leg-length discrepancies). This finding is very helpful in obese patients whose paraspinal prominence may be obscured by their subcutaneous adipose tissue.

103. What constitutes an abnormal scoliometer measurement?

The *scoliometer* (also called an *inclinometer*) is a type of protractor used to measure the vertebral rotation and rib prominence that is seen in scoliosis with the forward-bending test (Fig. 15.16). An angle of ≤5 degrees is usually

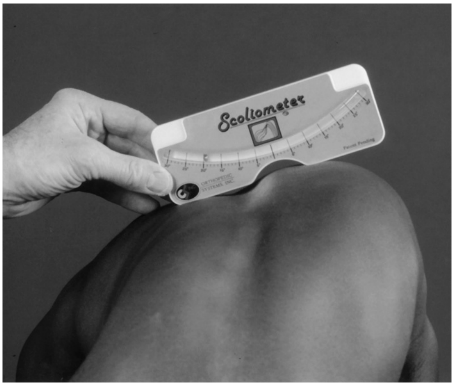


Fig. 15.16 Use of scoliometer demonstrating 20 degrees of trunk rotation. (From Dormans JP. *Pediatric Orthopaedics and Sports Medicine: The Requisites in Pediatrics.* Philadelphia, PA: Elsevier Mosby; 2004:150.)

insignificant, whereas an angle of ≥7 degrees warrants orthopedic referral and consideration of standing posteroanterior and lateral radiographs for more precise assessment of curvature. This is different from the measurement of the scoliosis made on radiographs, which is known as the Cobb angle (see question 104). Although it can vary dramatically, the Cobb angle is often about three times as large as the scoliometer measure. Usually orthopedists discuss the Cobb angle when describing scoliosis, and it is the Cobb angle that typically dictates treatment.

104. How is scoliosis measured by the Cobb method?

This is the standard technique used to quantify scoliosis in posteroanterior radiographs. One line is drawn along the vertebra tilted the most at the top of the curve, and another is drawn at the bottom of the curve. The curvature is represented by angle "a," which can be measured in two ways, as illustrated in Fig. 15.17.

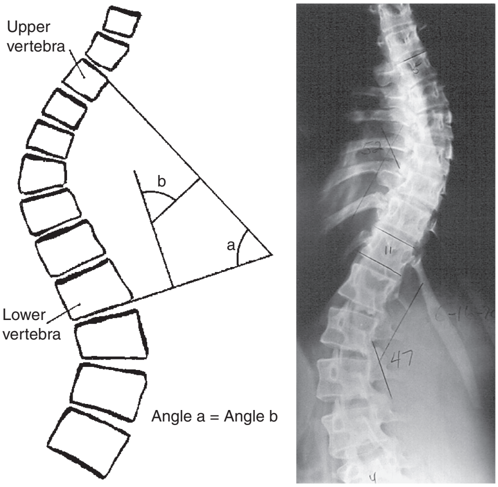


Fig. 15.17 Measurement of the Cobb angle. (From Kaz DS, Math KR, Groskin SA, eds. *Radiology Secrets.* Philadelphia, PA: Hanley & Belfus; 1998:321.)

105. When should children be referred to a specialist for evaluation of scoliosis?

In the adolescent age group (>10 years), referral has been recommended for scoliometer measurements ≥5 to 7 degrees or >10 degrees of Cobb angle. However, most nonsurgical interventions work best with smaller curves, so for patients at high risk for progression, earlier referral should be considered. This includes patients <10 years of age and those with a family history of severe scoliosis.

Johnson JP, Daniels AH, Grabel ZJ, et al. Referral for adolescent idiopathic scoliosis by pediatric primary care providers. *Clin Pediatr (Phila).* 2017;56(1):20–25.

106. Is scoliosis more common in boys or girls?

It depends on the age and the cause of the scoliosis. For idiopathic scoliosis seen in infancy, males outnumber females by a 3:2 margin. As age increases, females catch up, and by adolescence females are five to seven times more likely than males to have scoliosis.

107. How valuable are school-based screening programs for scoliosis?

This is controversial. About one-half of all states in the United States mandate school scoliosis screening. *Experts in favor* of these programs contend that reliable screening procedures exist and that early identification will lead to earlier nonoperative care and the prevention of progression and of the need for surgical intervention. *Opponents* argue that the low incidence of children requiring treatment, the low positive-predictive value of screening programs, and high numbers of children unnecessarily referred do not justify the screening programs. The U.S. Preventive Services Task Force has recommended against the routine screening of asymptomatic adolescents for idiopathic scoliosis. However, a joint statement by the AAP, American Association of Orthopedic Surgery, Scoliosis Research Society, and the Pediatric Orthopedic Society of North America strongly encourages that screening be done because of the effectiveness of nonsurgical interventions at preventing progression of smaller curves.

U.S. Preventive Services Task Force. Screening for adolescent idiopathic scoliosis. *JAMA.* 2018;319(2):165–172.

Scoliosis Research Society. Position statement–screening for the early detection of idiopathic scoliosis in adolescents. www.srs.org. Accessed January 23, 2020.

108. What is the natural history of adolescent idiopathic scoliosis (AIS)?

Untreated idiopathic scoliosis that is >50 degrees at skeletal maturity is likely to continue to progress throughout life. The rate of progression tends to be slow, on the order of 1 degree per year, but over the expected lifetime of the patient that could be ≥60 degrees of progression. However, even with this progression, AIS is generally not a fatal disease, and there is little excess mortality seen in the few long-term natural history studies. Only when curves are >90 to 100 degrees is there a clinically important effect on cardiopulmonary function. Some studies have shown psychosocial problems related to the patient's dissatisfaction with their appearance, but not all studies have reproduced this finding. Back pain may be increased in this population compared with age-matched norms, but there is no indication that surgery improves upon this.

Jada A, Mackel CE, Hwang SW, et al. Evaluation and management of adolescent idiopathic scoliosis: a review. *Neurosurg Focus.* 2017;43(4):E2.

Weinstein SL, Dolan LA, Spratt KF, et al. Health and function of patients with untreated idiopathic scoliosis: a 50-year natural history study. *JAMA.* 2003;289(5):559–567.

109. In children with idiopathic scoliosis, when is the decision for surgery made, and what type of surgery is typically performed?

As seen in the natural history, idiopathic scoliosis continues to progress throughout life once >**50 degrees**, so this is usually the criterion for surgery in AIS.

The surgery is usually a fusion procedure where the vertebrae involved in the curve are instrumented with metal implants and connected to a rod to correct the curve, balance the spine, and stabilize the bones to allow them to fuse to each other. Clearly, this eliminates motion and prevents growth in the operated segment of the spine. Most children with AIS are undergoing surgery in adolescence and as such do not have a lot of growth remaining. The height gained by straightening the spine typically offsets any potential loss of growth from fusing those vertebrae.

110. Are the spines of young children fused as well?

Not anymore. Scoliosis in toddlers and young children is one of the most difficult problems seen in pediatric orthopedics. Originally, these curves were corrected and fused, with the theory being that a short, straight spine is better than a longer, crooked one. However, long-term follow-up found that fusing spines before the age of 8 or 9 years resulted in small thoraxes and limited lung development. The result was that many of these patients were dying from respiratory insufficiency in early adulthood because their lungs were unable to keep up with the needs of their adult bodies.

111. So how are large curves in young children treated?

This is a challenging question with no good answer. Currently several options are available: casting, bracing, or growing implants. We know that fusing small spines is a bad idea, so implants that stabilize the spine while still allowing it to grow (sort of an internal brace) have been used with some success for a couple of decades. Current-generation "growing rods" attach to the ribs, spine, and/or pelvis. These rods then need to be lengthened periodically to compensate for the growth that is occurring in the spine and to maintain the correction of the scoliosis. Complication rates are high. On average, there is over one complication per patient over the duration of treatment, which can last years and require multiple surgeries. Some patients are candidates for a rod that can be lengthened in the office using a magnetically controlled gearing mechanism. This device has significantly reduced the number of surgeries these children undergo, but unfortunately, the rate of complications is similar to the rods that are lengthened surgically.

Bekmez S, Dede O, Yazici M. Advances in growing rods treatment for early onset scoliosis. *Curr Opin Pediatr.* 2017;29(1):87–93.

Hickey BA, Towriss C, Baxter G, et al. Early experience of MAGEC magnetic growing rods in the treatment of early onset scoliosis. *Eur Spine J.* 2014;23(Suppl 1):S61–S65.

112. Are casts still used to treat scoliosis?

The first fusion procedure for scoliosis was performed about 100 years ago, and for decades casts were used to stabilize the spine for months until the fusion could take hold. The advent of metal implants obviated the need for casts, but casting has become popular again as a treatment for scoliosis **in the very young**. A derotational casting technique has proven quite effective for many patients and can even be curative in some cases. Although no open surgery is involved, the casts do require traction under anesthesia and thus they are performed in the operating room.

Baulesh DM, Huh J, Judkins T, et al. The role of serial casting in early-onset scoliosis (EOS). *J Pediatr Orthop.* 2012;32(7):658–663.

Sanders JO, D'Astous J, Fitzgerald M, et al. Derotational casting for progressive infantile scoliosis. *J Pediatr Orthop.* 2009;29(6):581–587.

113. What other noninvasive techniques can be used for treating scoliosis?

Although standard physical therapy and chiropractic manipulation have not been shown to affect the natural history of scoliosis, there are **scoliosis-specific exercises (SSEs)** that focus on strengthening deep core muscles to hold the back in a straighter position (similar to therapy for people who slouch excessively). These are very specific exercise programs that require special training certification for the therapists who practice the techniques.

Negrini S, Donzelli S, Negrini A, et al. Specific exercises reduce the need for bracing in adolescents with idiopathic scoliosis: a practical clinical trial. *Ann Phys Rehabil Med.* 2019;62(2):69–76.

114. Is bracing an effective treatment for scoliosis?

There has long been a history of bracing in the orthopedic literature, and the results of studies have been somewhat mixed. Also, the quality of many of these studies has been low, and many orthopedists were unsure if bracing was an effective treatment. However, a 2013 multicenter study found dramatic improvements in children who were braced compared with unbraced controls. This BrAIST (Bracing in Adolescent Idiopathic Scoliosis Trial) study is the first to prove the effectiveness of bracing in premenarchal adolescent girls.

Khan MJ, Srinivasan VM, Jea AH. The history of bracing for scoliosis. *Clin Pediatr (Phila).* 2016;55(4):320–325.

Weinstein SL, Dolan LA, Wright JG, Dobbs MB. Effects of bracing in adolescents with idiopathic scoliosis. *N Engl J Med.* 2013; 369(16):1512–1521.

115. What are the risk factors for the progression of idiopathic scoliosis?

Idiopathic scoliosis is a growth phenomenon, and the rate of progression of the curve is proportional to the **rate of growth**. This is why many curves become clinically apparent in adolescence just after the growth spurt. Therefore the risk for progression is greater in younger children (who have more growth remaining), and the larger the curve, the more likely it is to progress. Interestingly, osteopenia has also been found to be a risk factor for progression. Most other risk factors for progression are a surrogate for growth remaining, such as skeletal age and menarchal status.

KEY POINTS: SCOLIOSIS

1. Scoliosis of $>$10 degrees is relatively common (1% to 2%), but progression to $\geq$25 degrees and requiring treatment is rare.
2. Bracing does not permanently correct scoliosis, but it can prevent progression.
3. Establishing the maturity level of the skeleton is important because the risk for progression is increased with immaturity.
4. In adolescents, progressive curves are seven times more likely to appear in girls than in boys.
5. All scoliosis is not idiopathic: assess for limb-length discrepancy, congenital anomalies, and neurologic abnormalities.

116. What diagnosis should you consider in a teenage male with very poor posture that is not flexible?

Scheuermann kyphosis. This is a wedge-shaped deformity of the vertebral bodies of unclear etiology that causes juvenile kyphosis (abnormally large dorsal thoracic or lumber curves). Common in teenagers, it is distinguished from simple poor posture ("postural round-back deformity") by its sharp angulation and inability to correct by having the patient stand up straight or lie on top of a bolster. X-ray studies reveal anterior vertebral body wedging and irregular erosions of the vertebral end plate. Treatment consists of exercise, bracing, and, rarely, surgical correction (for severe, painful deformities).

117. What is the difference between spondylolysis and spondylolisthesis?

- *Spondylolysis* is a condition in which there is a *defect in the pars interarticularis* (vertebral arch) of a vertebra that is most common at L5. This can be a congenital problem but is commonly seen as a stress fracture in athletes who do a lot of hyperextension of the lower back (classically gymnasts and football offensive linemen).
- *Spondylolisthesis* is a condition (often resulting from spondylolysis) that is characterized by *forward slippage* of one vertebra on the lower vertebrae. Pain is the most common presenting symptom for both conditions. The etiology is unclear, but various theories relate it to hereditary factors, congenital predisposition, trauma, posture, growth, and biomechanical factors. Treatment includes watchful waiting, limitation of activity, exercise therapy, bracing, casting, and surgery, depending on the patient's age, the magnitude of the slippage, the extent of pain, and the predicted likelihood of progression of the deformity.

Foreman P, Griessenauer CJ, Watanabe K, et al. L5 spondylolysis/spondylolisthesis: a comprehensive review with an anatomic focus. *Childs Nerv Syst.* 2013;29(2):209–216.

SPORTS MEDICINE

118. A 12-year-old baseball player presents complaining of elbow pain. What diagnosis do you need to consider?

Little League elbow, an *apophysitis* of the *medial epicondyle* of the elbow, is a tension injury to the growth plate seen in throwers' elbows. Treatment includes rest and avoiding all throwing activities for a minimum of 4 to 6 weeks, followed by gradual resumption of throwing under the close guidance of a therapist and/or coach.

119. Which is more stressful for a baseball pitcher's elbow: throwing curveballs or fastballs?

Conventional wisdom has held that curveballs are more stressful on the thrower's elbow than fastballs, and there are recommendations that curveballs not be thrown until an athlete is approaching skeletal maturity, around 14 years of age. However, recent research has found that the amount of **mechanical stress on an elbow is not different** when throwing a curveball or fastball. There may be other reasons to limit or delay throwing curveballs in younger athletes, but increased stress at the elbow, it seems, is not one of them.

Nissen CW, Westwell M, Ounpuu S, et al. A biomechanical comparison of the fastball and curveball in adolescent baseball pitchers. *Am J Sports Med.* 2009;37(8):1492–1498.

120. How can elbow and shoulder injuries be prevented in pitchers?

The use of **pitch counts** to protect the arms of throwers at all levels of baseball from Little League to the majors has come into the spotlight in recent years. There is evidence showing that pitch count is more important than the type of pitch thrown in protecting the elbow. Multiple youth organizations, in conjunction with U.S. Major League Baseball, have standardized the number of pitches allowed and the amount of rest mandated between pitching days based on age.

Tjoumakaris FP, Pepe MD, Bernstein J. Eminence-based medicine versus evidence-based medicine: it's okay for 12-year-old pitchers to throw curveballs; it's the pitch count that matters. *Phys Sportsmed.* 2012;40(3):83–86.

Major League Baseball. Guidelines for youth and adolescent pitchers: Pitch Smart USA. www.mlb.com. Accessed January 23, 2020.

121. Do meniscal tears occur in younger children?

Rarely do meniscal tears occur before the age of 12 years. An exception is a child with a discoid meniscus, which is a congenitally abnormal meniscus shaped like a hockey puck instead of a "C." Because this places portions of the meniscus in the weight-bearing portion of the knee (for which the meniscus is not designed), the meniscus will eventually tear and become symptomatic. Meniscal tears in children not associated with a discoid meniscus are typically associated with significant injuries. They produce pain, swelling, and limping. Be sure to look for an associated injury to the anterior cruciate ligament (ACL).

122. If a ninth-grade soccer player with knee swelling "felt a pop" while scoring a goal, what are three possible diagnoses?

A pop or snap sensation in the setting of acute knee injury is usually associated with the following:

- **ACL injury**
- **Meniscal injury**
- **Patellar subluxation**

123. How is meniscal integrity assessed on examination?

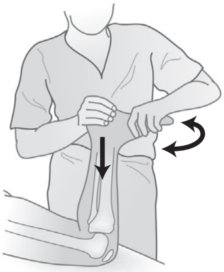
The **Apley compression test** and **McMurray test**. The Apley test uses compression of the knee while the patient is in a prone position; pain in the knee suggests meniscal injury. The McMurray test assesses lateral and medial tears by applying valgus stress/internal rotation and varus stress/external rotation, respectively, while feeling for pops/clicks and tenderness over the joint line. If present, these findings could indicate injury (Fig. 15.18).

124. What is the typical mechanism for an ACL tear?

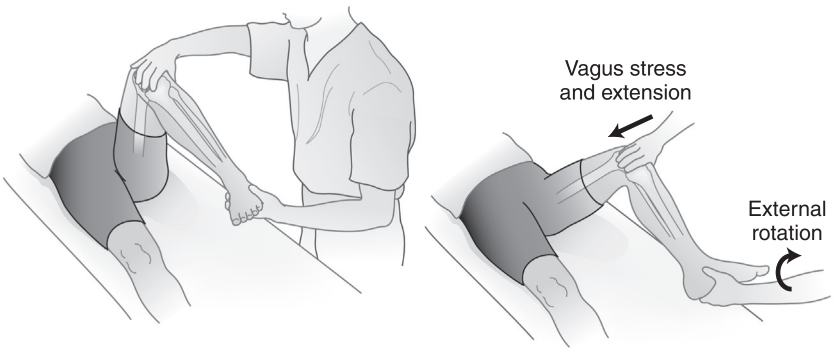
The ACL sits in the knee joint and prevents the tibia from subluxing anteriorly out from under the femur. This ligament is under stress when weight is applied to a slightly flexed knee and when rotation and a valgus stress (a force pushing the knee toward the midline) is applied to the knee at the same time. It is at this point that the ligament is most susceptible to tearing. This combination of forces typically occurs when an athlete lands on the leg and tries to change direction.

125. How is ACL stability tested on examination?

The **Anterior drawer test** and **Lachman test**. Both assess any possible abnormal forward movement of the tibia with the thigh/femur and foot stabilized. Excessive movement compared with the opposite knee suggests ACL injury (Fig. 15.19).

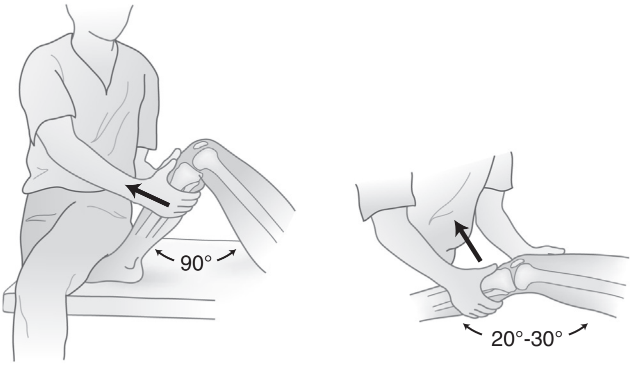


Apley compression test



McMurray test

Fig. 15.18 The *Apley compression test* is performed with the patient prone and the examiner's knee over the patient's posterior thigh. The tibia is externally rotated while a downward compressive force is applied over the tibia. The *McMurray test* is performed with the patient supine and the examiner standing on the side of the affected knee. (From Kleigman RM, Stanton BF, Schor NF, et al. *Nelson Textbook of Pediatrics.* 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:2415.)



Anterior drawer test **Lachman test**

Fig. 15.19 The *anterior drawer test* is performed with the patient supine and the knee in 90 degrees of flexion. The *Lachman test* is conducted with the patient supine and the knee flexed 20 to 30 degrees. (From Kleigman RM, Stanton BF, Schor NF, et al. *Nelson Textbook of Pediatrics.* 19th ed. Philadelphia, PA: Elsevier Saunders; 2011:2415.)

126. Why do girls and young women seem to be more susceptible to ACL tears than their male counterparts?

Many reasons have been shown to be associated with an increased risk for ACL tears in females, a risk three to eight times higher than in males. There are **anatomic factors,** such as a narrower intercondylar notch in the knee and wider pelvises than males; **biochemical factors,** such as increased estrogen**,** which makes ligaments more elastic; and **neuromuscular factors** in the way women activate muscles during jumping and landing. Researchers from Oregon have described several upstream factors as well that include chronic fatigue (three times more likely in high school girls than boys) and dietary problems that range from poor nutritional intake to frank eating disorders.

Elliot DL, Goldberg L, Kuehl KS. Young women's anterior cruciate ligament injuries: an expanded model and prevention paradigm. *Sports Med.* 2010;40(5):367–376.

127. Are ACL tears treated differently in children, adolescents, and adults?

A resounding **yes**. Traditional ACL reconstruction procedures involve drilling a large tunnel across where the physis would be in the proximal tibia and distal femur. In children with open physes, the concern for growth arrest is great. Current recommendations are generally for using a *physeal-sparing* technique in prepubescent children, which is not as stable as traditional techniques and technically more difficult to perform. For younger adolescents a *transphyseal* reconstruction is permitted, but the graft is all soft tissue, and the sutures or screws used to stabilize the graft are placed far from the growth plate. In older adolescents, a standard transphyseal technique is used, although no bone is placed across the growth plate (a technique sometimes used in adults).

Vavken P, Murray MM. Treating anterior cruciate ligament tears in skeletally immature patients. *Arthroscopy.* 2011;27(5):704–716.
Finlayson CJ, Nasreddine A, Kocher MS. Current concepts of diagnosis and management of ACL injuries in skeletally immature athletes. *Phys Sportsmed.* 2010;38(2):90–101.

128. Are there ways to prevent ACL tears?

Most ACL tears are a result of noncontact plays (that is, landing a jump or making a cut on the field, rather than being tackled or hit). This mechanism seems apropos for prevention programs. The number of prevention programs has exploded across the country in recent years, typically involving **neuromuscular training exercises** to retrain athletes the best way to jump, land, and cut. Neuromuscular training and strength training at younger ages have shown promise in reducing ACL injuries.

Nessler T, Denney L, Sampley J. ACL injury prevention: what does research tell us? *Curr Rev Musculoskeletal Med.* 2017;10(3):281–288.

129. A teenager has chronic knee pain, swelling, and occasional "locking" of the knee joint, and his x-ray reveals increased density and fragmentation at the weight-bearing surface of the medial femoral condyle. What condition does he likely have?

Osteochondritis dissecans. In this disease, there is *focal necrosis* of a region of subchondral bone, typically in the lateral half of the medial femoral condyle. The cause is unknown, but antecedent trauma is common, and children (usually boys) with this condition are typically very active. These cases present with activity-related pain; locking, buckling, and stiffness may be seen as well. A plain radiograph can reveal the diagnosis, but MRI is more sensitive when the clinical suspicion is high and radiographic findings are equivocal. Extended immobilization and activity restriction are the primary treatments in skeletally immature patients who have a favorable natural history. The lesions typically heal without surgery. For older adolescents and skeletally mature individuals, surgery is frequently required to stabilize the lesion and encourage healing. If the fragment does not heal, it may detach and become a loose body. This is a major problem because the lost articular cartilage cannot be replaced and the risk for arthritis is high.

Bauer KL, Polousky JD. Management of osteochondritis dissecans lesions of the knee, elbow and ankle. *Clin Sports Med.* 2017; 36(3):469–487.

130. What is the most likely diagnosis if a 12-year-old basketball player has painful swelling below both knees?

Osgood-Schlatter disease. This is a *traction apophysitis* and results from repetitive stress (pull of the patellar tendon) on the tibial tubercle, which is connected to the tibial shaft through a cartilaginous plate. The cartilage is unable to handle the tensile forces created by the quadriceps muscle, and it hypertrophies and becomes inflamed. This process often occurs around the time of the adolescent growth spurt and is related to the level of physical activity. Physical examination reveals tenderness to palpation and a very prominent tibial tubercle. The pain is exacerbated with resisted knee extension.

Appropriate clinical management includes the judicious use of anti-inflammatory medications, restricted activities, quadriceps stretching and strengthening, and cross-training. The condition is usually self-limited and resolves with skeletal maturity, although the bump remains. Immobilization, which may lead to disuse atrophy, is rarely necessary.

Circi E, Atalay Y, Beyzadeoglu T. Treatment of Osgood-Schlatter disease: review of the literature. *Musculoskelet Surg.* 2017; 101(3):195–200.

131. What is the likely diagnosis in a fifth-grade football player with heel pain and a positive “squeeze test”?

Sever disease, or *apophysitis of the calcaneus*. Caused by traction on the calcaneus at the insertion sites of the gastrocnemius-soleus muscles, microavulsions occur where bone meets cartilage. Pain is reproduced with compression of the medial and lateral aspects of the heel (the “squeeze test”). Treatment involves Achilles stretching, viscoelastic heel cups, and NSAIDs. Failure to improve suggests a possible calcaneal stress fracture, and immobilization may be required.

Soprano JV, Fuchs SM. Common overuse injuries in the pediatric and adolescent athlete. *Clin Pediatr Emerg Med.* 2007;8:8–11.

132. Which sports injuries are the most common in school-aged children and adolescents?

About 75% of injuries in school-aged children involve the lower extremities, and a majority of injuries to the knee and ankle are reinjuries as a result of incomplete healing from a previous problem. Contusions and sprains are the most common types of injury, with fractures and dislocations accounting for an additional 10% to 20%. Cranial injuries are the most common cause of sports fatality. Adolescent boys who participate in contact team sports, particularly football and wrestling, are at the highest risk for injuries. Among girls, softball and gymnastics have the highest injury rate. Only 10% of sports injuries are caused by an opponent; most injuries are caused by stumbling, falling, or misstepping. The latter finding suggests that improving intrinsic factors (e.g., raising the level of physical fitness, avoiding overuse, and strengthening joint stability) may be more important for the prevention of injuries than external factors (e.g., rule changes, equipment).

TRAUMA

133. What fracture patterns are unique to children?

Children can suffer from **physeal (growth plate) fractures**, **buckle fractures**, **greenstick fractures,** and **plastic deformation** injuries. Most fractures in children incorporate one or more of these patterns.

134. What is a buckle fracture?

Children’s bones are softer and more plastic than adult bones. Their bones can bend without actually breaking. A *buckle (or torus) fracture* occurs when a bone is bent (usually as a result of a fall) and compressive forces cause the cortex to actually buckle out, causing a bump in the bone. This is analogous to what happens to the sheet metal in a car involved in a collision. Although this is a fracture, the bone is still in one piece and stable, which is why these fractures are often diagnosed a week or two after injury, much to the surprise and chagrin of the parents who had been ignoring their child’s plaintive complaints.

135. What is a greenstick fracture?

A *greenstick* is an **incomplete fracture of a long bone**. It is called this because the fracture pattern is similar to what happens when you try to snap a still-living branch (or green stick) in half: the branch will break on one side but not all the way through. Similarly, in a greenstick fracture, only one cortex fractures while the other cortex remains intact, although usually bent.

136. What does plastic deformation mean?

The softness, or plasticity, of a child’s bones allows them to bend without breaking. When you take a metal rod and bend it just a little, it tends to spring back to its original position. However, if you bend it more, it may spring back, but not all the way, leaving you with a bent rod. The same thing can happen in children’s bones. Adult bones are much more rigid and do not really bend before breaking. It is important to realize that plastically deformed bones *do not remodel* (reshape themselves with growth) because there is no healing response as there is when the bone is actually cracked. Therefore patients with significant plastic deformation may require the fracture to be straightened (in the operating room or under sedation).

137. What is an open fracture?

In an *open fracture,* the **fracture site communicates with the external environment**, usually as a result of the bone piercing the skin. Oftentimes the bone pokes out, then falls back beneath the skin, so any laceration of a fracture site must be presumed to be an open fracture until proven otherwise. Open fractures have higher incidence of infection and a higher degree of soft tissue damage compared with closed fractures.

138. What is the difference between open and closed reductions of fractures?

To reduce a fracture means to realign the bone to its original shape. A *closed reduction* occurs by simply pushing on the bone and holding it in place with a splint or cast. This may be done in the emergency department or the operating room and very often with some form of anesthesia. An *open reduction* implies that an incision is required to expose the fracture site and help realign the bone. An internal implant will often be utilized to stabilize the bone and maintain alignment during healing.

139. What is a toddler fracture?

A toddler fracture is a fracture of the tibia in a child 9 months to 3 years old as a result of low-energy rotational forces. Typically, these fractures have a spiral appearance and are not displaced. The fibula is rarely fractured. The child will limp or more commonly refuse to bear weight. If the child is comfortable at rest, no immobilization is required, but some children (and families) will be more comfortable in a cast or splint for around 2 to 3 weeks.

140. How are growth-plate fractures classified?

The Salter-Harris classification of growth-plate (physis) injuries (Fig. 15.20) was devised in 1963:

- **Type I:** Epiphysis and metaphysis separate; usually no displacement occurs as a result of the strong periosteum; radiograph may be normal; tenderness over the physis may be the only sign; normal growth after 2 to 3 weeks of cast immobilization
- **Type II:** Fragment of metaphysis splits with epiphysis; usually closed reduction; casting is for 3 to 6 weeks (longer for lower extremity than upper extremity); growth usually not affected, except distal femur and tibia
- **Type III:** Partial plate fracture involving a physeal and epiphyseal fracture to the joint surface; occurs when growth plate is partially fused; closed reduction more difficult to achieve
- **Type IV:** Extensive fracture involving epiphysis, physis, metaphysis, and joint surface; high risk for growth disruption unless proper reduction (usually done operatively) is obtained
- **Type V:** Crush injury to the physis; high risk for growth disruption

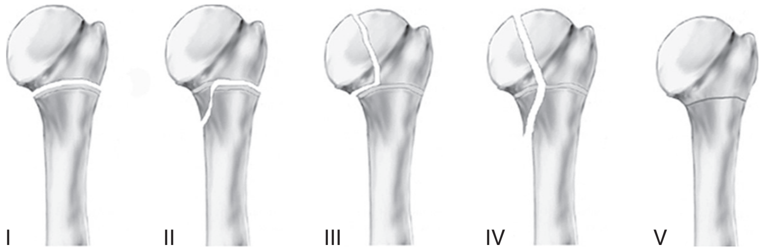


Fig. 15.20 Salter-Harris classification. (From Katz DS, Math KR, Groskin SA, eds. *Radiology Secrets.* Philadelphia, PA: Hanley & Belfus; 1998:403.)

141. What are the sequelae of growth-plate fractures?

Most *growth-plate fractures* fortunately heal without incidence. However, if there is an injury to the growth plate, a growth disturbance may occur caused by the formation of a bony bridge or bar at the site of physeal damage. If there is damage to the entire physis, premature physeal closure occurs, with resulting longitudinal growth arrest. Asymmetric closure leads to angular deformity of the limb. Fractures of the distal femoral physis are particularly prone to premature closure.

142. What is the most common cause of a pathologic fracture?

Also called *secondary fractures,* these are fractures through a bone weakened by a pathologic process. The most common such fracture is through **unicameral bone cysts** (simple bone cysts). These cysts usually occur in the metaphysis of a long bone, most frequently the humerus. They occur predominantly in males, are usually asymptomatic (unless a fracture occurs), are centrally located in the bone, and are often quite large.

143. In a patient with suspected fracture, what are the key points on physical examination?

Assess “the five Ps” in the affected extremity:

- **P**ain and point tenderness
- **P**ulse (distal to the fracture)—to evaluate vascular integrity
- **P**allor—to evaluate vascular integrity
- **P**aresthesia (distal to the fracture)—to assess for sensory nerve injury
- **P**aralysis (distal to the fracture)—to assess for motor nerve injury

Examine for pain above and below the suspected injury site, as multiple fractures can occur in the same limb. The involved extremity should also be carefully examined for deformity, swelling, crepitus, discoloration, and open wounds. A primary concern in any evaluation is a distal neurovascular compromise, which may require immediate surgical intervention. Although the neurologic examination can be challenging in the setting of pain, especially in the younger child who is not cooperative, it is very important to do as thorough an examination as possible.

144. What are the signs of compartment syndrome?

The five Ps noted in the preceding question are seen in impending or established *compartment syndrome* in which swelling is causing distal ischemia. However, the most important symptom is **pain**—especially pain that does not respond to medication and pain with passive range of motion of the digits (fingers or toes) distal to the fracture. If one waits for numbness and paralysis to make the diagnosis of compartment syndrome, it is too late—permanent damage has likely been done. Compartment syndrome is often unrecognized in unconscious patients, so a high index of suspicion must be maintained in patients with severe injuries and an altered mental status. In addition, a frightened young child or infant may be very difficult to examine. If there is any concern about compartment syndrome, the compartment pressures must be measured.

145. What is the treatment of compartment syndrome?

Compartment syndrome is a true orthopedic emergency. Increased pressure in a compartment is relieved by incising the skin and fascia encompassing the involved compartment. The wound is left open and covered with sterile dressing until swelling decreases. Dressing changes, débridements and partial wound closure are usually done in the operating room every day or 2 until the skin can be closed. In some cases, skin grafts are necessary.

146. How do you treat a simple fracture of the clavicle?

These fractures are best managed with a **sling and activity restriction**. Union occurs in 2 to 4 weeks, but the sling may be removed once the child is comfortable. The residual bump (fracture callus) may take up to 2 years to smooth out (remodel), but there always may be some bump left, especially in older children.

Stepanyan H, Gendelberg D, Hennrikus W. Management of simple clavicle fractures by primary care physicians. *Clin Pediatr (Phila).* 2017;56(5):467–471.

147. Is surgery ever indicated for clavicle fractures?

Never say never, but surgical treatment of clavicle fractures in children is a very rare event. Traditionally, surgery has been considered necessary in children in only a few extreme scenarios: open fractures, neurovascular injury, or skin compromise. In the adult literature, there has been growing enthusiasm supporting surgical fixation of fractures with significant shortening of the bone (>2 to 3 cm), as these can cause problems with weakness and deformity in the affected shoulder. However, there is no similar literature to support surgery in a pediatric population and no study that examines functional outcomes after surgery compares results with those treated nonsurgically. All studies in children show close to a 100% healing rate for clavicular fractures without surgery. Even studies that look at outcomes with surgery reveal that these cases represent only 1% of all clavicle fractures seen.

Vargas-Vila MA, Mehlman CT, Pennock AT. The community orthopaedic surgeon taking trauma call: pediatric midshaft clavicle fracture pearls and pitfalls. *J Orthop Trauma.* 2019;33(Suppl 8):S1–S5.

Namdari S, Ganley TJ, Baldwin K, et al. Fixation of displaced midshaft clavicle fractures in skeletally immature patients. *J Pediatr Orthop.* 2011;31(5):507–511.

148. A teenager who punches a wall in anger typically incurs what fracture?

Boxer fracture. This is a fracture of the distal fifth metacarpal, usually with apical dorsal angulation (Fig. 15.21). Up to 35 degrees of angulation can be accepted without compromise of function. Reduction often requires pin fixation.

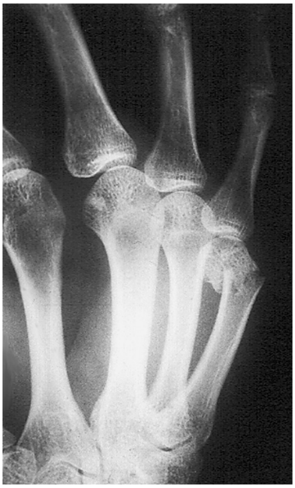


Fig. 15.21 Boxer fracture with fracture of fifth (and fourth) metacarpal with volar displacement of the distal fragments after a punching injury. (From Katz DS, Math KR, Groskin SA, eds. *Radiology Secrets.* Philadelphi[illegible] Hanley & Belfus; 1998:440.)

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149. Children who fall on outstretched arms often suffer what type of fractures?

Colles fractures. This is a group of complete fractures of the distal radius with varying displacement of the distal fragment. The fall, with the hand outstretched, wrist dorsiflexed, and forearm pronated, often results in a classic "dinner-fork" deformity with fixed curvature of the wrist on examination (Fig. 15.22).

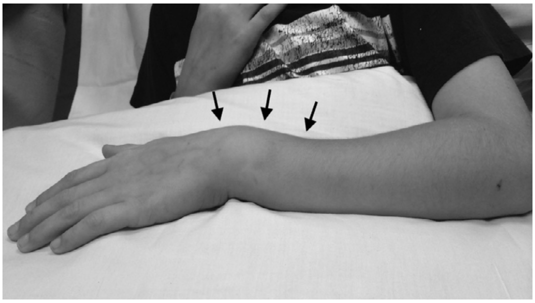

Fig. 15.22 Colles fracture with dinner-fork deformity of left forearm *(arrows)*. (From Kardouni JR. Child with dinner fork deformity. Distal radius fracture. *Ann Emerg Med.* 2016:67(2):165.)

150. What does the presence of the posterior fat pad on an elbow x-ray suggest?

Of the two fat pads that overlie the elbow joint, only the anterior one is visible on a lateral x-ray. If fluid accumulates in the joint space, as it does in cases involving bleeding, inflammation, or fracture, the fat pads are displaced upward and outward. The position of the anterior pad changes, and the posterior pad becomes visible. In the setting of acute trauma, the presence of a posterior fat pad is associated with a nearly 75% chance of **occult fracture**, and the elbow should be immobilized in a cast or splint with close follow-up scheduled. The most common injuries would be a radial head fracture and a nondisplaced supracondylar humerus fracture.

151. In a teenager with wrist trauma, why is palpation of the anatomic "snuff box" a critical part of the physical examination?

The *anatomic snuff box* (the in-pouching formed by the tendons of the abductor pollicis longus and extensor pollicis longus when the thumb is abducted [in hitchhiker fashion]) sits just above the scaphoid bone. The scaphoid is the carpal bone most commonly fractured, and it is at high risk for nonunion or avascular necrosis due to its precarious blood supply. Snuff box tenderness, pain on supination with resistance, and pain on longitudinal compression of the thumb should increase suspicion for **fracture of the scaphoid bone**. Even when an x-ray is negative, if there is significant snuff box tenderness, a fracture should be suspected and the wrist and thumb immobilized. A repeat x-ray in 2 to 3 weeks may better reveal a fracture. The use of CT or MRI can be used to more reliably identify a scaphoid fracture when the plain film is negative and the clinical suspicion is high.

152. Name the eight carpal bones of the wrist.

Disdaining some of the classic (many risqué) mnemonics, remember what will happen if a wrist fracture is missed: **S**inister **L**awyers **T**ake **P**hysicians **T**o **T**he **C**ourt **H**ouse, which helps recall the bones (in order of proximal to distal, lateral to medial): **s**caphoid, **l**unate, **t**riquetrum, **p**isiform, **t**rapezium, **t**rapezoid, **c**apitate, and **h**amate.

153. In pediatric fractures, what amount of angulation is acceptable before reduction is recommended?

Acceptable angulation or displacement **varies with a child's age**. Younger children have remarkable healing potential to remodel with minimal to no residual deformity or limitation of rotation. As a rule, in children up to 8 years of age, as much as 30 degrees of angulation *in the plane of motion* will heal satisfactorily without reduction. This means that a fracture that is flexed or extended in the wrist (in the direction the wrist typically moves) can be expected to model well. However, displacement with angulation toward the radius or ulna will not remodel so reliably, and rotational malalignment will not remodel at all. The degree of remodeling diminishes with age, with increasing distance from the growth plate, and with less growth remaining. In general, fractures closer to the growth plate will remodel more readily than midshaft fractures.

154. In which fractures does remodeling of bone typically *not* occur?

Remodeling, or reshaping of the bone to its original configuration, is a common phenomenon in pediatric fractures and allows orthopedists to accept some residual deformity and treat many fracture patterns without surgery. Remodeling occurs most readily when the fracture is close to the growth plate and the deformity is in the plane of motion (e.g., a distal femur fracture is bent in flexion as opposed to being in varus or valgus). Interestingly, **extension-type supracondylar humerus fractures**, the most common surgically treated elbow fracture in children, do not remodel very well even though they are close to the physis and the deformity is in the plane of motion (extension usually). The following fractures also have a low chance of remodeling and may require reduction: **intra-articular fractures** (these must always be reduced anatomically to preserve joint function); **plastic deformation** (see earlier), and **fractures with excessive shortening or rotation**. Angulation and translation deformities may remodel, but if the severity is too great, they may not remodel completely and may leave residual deformity and dysfunction.

155. How long should fractures be immobilized?

Children's fractures generally heal more quickly than their counterparts in adults. The exact length of immobilization depends on several variables, including the child's age, the location of the fracture, and the type of treatment. As a rule of thumb, physeal, epiphyseal, and metaphyseal fractures heal more rapidly than diaphyseal fractures. On average, epiphyseal, physeal, and metaphyseal fractures heal in children within 3 to 5 weeks, whereas diaphyseal fractures may heal within 4 to 6 weeks. Fractures of the tibial shaft, however, can take even longer to heal**,** as this is a watershed area for blood supply, and 8 to 10 weeks is not an unusual time to heal.

Acknowledgment

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CHAPTER 16

PULMONOLOGY

Andrei Constantinescu, MD, PhD

ALLERGIC RHINITIS

1. How common is allergic rhinitis?

Very common. Ten percent to 30% of children and adults in the developed world experience allergic rhinitis, which is the most common manifestation of allergic disease and one of the most common chronic diseases of childhood.

2. In addition to chronic or recurrent nasal congestion, what features on history and physical examination suggest allergic rhinitis?

- "Allergic facies": Open mouth, midface hypoplasia
- "Allergic nasal crease": Nasal crease on bridge of the nose as a result of chronic upward rubbing with the palm of the hand (the "allergic salute")
- Diminished sense of taste and smell
- Dental malocclusion
- Allergic "shiners" (dark circles under the eyes)
- Multiple infraorbital folds
- Cobblestoning of the posterior oropharynx (Fig. 16.1)
- Pale, boggy appearance of the nasal mucosa

Tharpe CA, Kemp SF. Pediatric allergic rhinitis. *Immunol Allergy Clin North Am.* 2015;35(1):185–198.

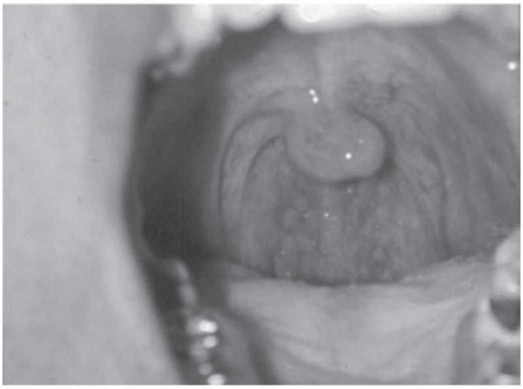

Fig. 16.1 Cobblestone appearance of the posterior pharynx from postnasal drip. (From Terasaski G, Paauw DS. Evaluation and treatment of chronic cough. *Med Clin North Am.* 2014;98:391-403.)

3. What are three early-life risk factors for allergic rhinitis?

- Male gender (females have a higher incidence of rhinitis in adulthood)
- Not having early contact with siblings at home or children in day care
- Not having early contact with pets or not living on a farm

Matheson MC, Dharmage SC, Abramson MJ, et al. Early-life risk factors and incidence of rhinitis: results from the European Community Respiratory Health Study—An international population-based cohort study. *J Allergy Clin Immunol.* 2011;128(4):816–823.

4. How does the time of year help identify the potential cause of allergic rhinitis?

Tree pollen is usually associated with the onset of the growing season. After local tree pollination, grass pollens appear; this may occur earlier in locales where there are short winters. Weed pollen other than ragweed is associated with the late-summer pollen peak. In the autumn, ragweed is the major pollen allergen. It pollinates from mid-August until the first freeze in most of the United States. Counts are especially high in eastern and central North America. Fungal aeroallergens span the growing season. Relative concentrations of household animal allergens, dust mites, and indoor fungi generally increase when doors and windows are closed. However, dust mites and molds proliferate in areas of high humidity and may cause perennial symptoms.

Naclerio R, Solomon W. Rhinitis and inhalant allergens. *JAMA.* 1997;278(22):1842–1848.

5. When are allergy blood tests used?

- A patient is taking a medication that blocks allergy skin testing, such as an antihistamine that cannot be stopped for at least 3 days.
- A patient has a skin condition such as eczema or psoriasis without sufficient unaffected areas to do skin testing.
- Blood testing would be better tolerated, such as in an infant or young child.

American College of Allergy, Asthma and Immunology. www.acaai.org. Accessed March 11, 2020.

6. What are the pros and cons of skin testing versus in vitro testing (i.e., quantification of allergen-specific immunoglobulin E [IgE] in patient's serum) for allergies?

In vitro tests

- No risk for anaphylaxis
- Results not influenced by medications (e.g., antihistamines), dermatographism, or extensive dermatologic disease
- More costly
- Better predictive value for some common food allergens

Skin testing

- Less costly
- More sensitive than in vitro tests
- Results immediately available

7. What are the recommended treatments for children with allergic rhinitis?

- **Environmental control** measures for allergen avoidance are the mainstay of treatment. Relevant allergens are recommended for exposure reduction on positive skin or serum-specific IgE testing correlated with the presence of symptoms on allergen exposure.
- **Pharmacotherapy**, including nasal corticosteroid sprays, antihistamines (given orally or by nasal spray), oral antileukotrienes, or combinations of these medications are effective treatments.
- **Immunotherapy** is reserved for those with persistent symptoms despite the previous treatment and for those who want control of symptoms with fewer medications.

American Academy of Allergy, Asthma and Immunology. www.aaaai.org. Accessed March 11, 2020.

KEY POINTS: ALLERGIC RHINITIS

1. History (symptoms, family history, and worsening with environmental exposure) is the key to diagnosis.
2. With two atopic parents, the risk to the child is 50% to 70%.
3. Sensitivity of testing ranks as follows: intradermal (may yield false-positive results) $>$ skin prick $>$ in vitro allergen-specific IgE quantification.
4. IgE ImmunoCAP testing is indicated in patients with severe skin disorders or those unable to temporarily discontinue H_1-blocking antihistamines.
5. Allergic features include shiners (dark circles under eyes), increased infraorbital folds, transverse nasal bridge crease, boggy pale-blue nasal mucosa, and cobblestoning of conjunctiva and posterior oropharynx.
6. Immunotherapy should be considered when allergen avoidance and pharmacotherapy have produced suboptimal results.

8. What are the major indoor (year-round) allergens?

House dust mites (HDMs), **animal dander**, **cockroach**, and **molds**.

9. How can HDM concentrations be minimized?

Allergens from HDMs are among the most common triggers for allergic rhinitis and asthma. They are found throughout homes, but accumulate in bedding, soft furnishings, and carpet. HDM allergen reduction methods include the following:

- Encasing pillows, mattresses, and box springs in allergen-proof, zippered covers (plastic or fine woven fabric). Although not effective as a single measure, there is evidence these covers may be of benefit when used as part of an extensive bedroom-based dust mite allergen reduction program.

- Bedding may be washed in hot (131°F [55°C]) water. Drying the bedding in high heat in a dryer is an alternative that may prevent scalding injuries in children from having the water heater temperature raised above 120°F (50°C).
- Humidity should be reduced indoors to $\leq$45% using a dehumidifier and/or air conditioning with the windows closed.
- Wall-to-wall carpeting should be removed as much as possible and replaced with throw rugs. These should be regularly washed or dry-cleaned.

Wilson JM, Platts-Mills TAE. Home environmental interventions for house dust mite. *J Allergy Clin Immunol Pract.* 2018;6(1):1–7.
Sheikh A, Hurwitz B, Nurmatov U, et al. House dust mite avoidance measures for perennial allergic rhinitis. *Cochrane Database Syst Rev.* 2010;(7):CD001563.

10. How can you decrease cat allergen in the home?

- Remove upholstered furniture, carpet, and other sources harboring the allergen.
- Use high-efficiency particulate air (HEPA) filters and vacuum cleaners.
- Wash the cat regularly if feasible.
- Consider a "felinectomy."

11. Is there truly a dog breed that is "hypoallergenic"?

Alas, the hypoallergenic dog appears to be a **myth**. Although certain dogs (e.g., poodles, Spanish waterdogs, Airedale terriers, and a hybrid, the Labradoodle) are commonly marketed as "hypoallergenic," comparison of the quantity of the dog allergen (Can f 1, an allergen specific to dogs) in hair and coat samples and in the surrounding surface environment found no differences compared with control breeds. In the United States, about 78 million dogs occupy homes, so this is not good news to the 20% of the general population who may be allergic to dogs.

Vredegoor DW, Willemse T, Chapman MD, et al. Can f 1 levels in hair and homes of different dog breeds: lack of evidence to describe any dog breed as hypoallergenic. *J Allergy Clin Immunol.* 2012;130(4):904-909.e7.

12. Which children should be considered for immunotherapy?

Allergen immunotherapy is an effective treatment for allergic rhinitis, asthma, and the prevention of venom anaphylaxis. It also may be of benefit in atopic dermatitis. For allergic rhinitis and allergic asthma, immunotherapy should be considered in patients who (1) are not well controlled despite attempts at allergen exposure reduction and pharmacotherapy or (2) in patients who wish to take less medication. Subcutaneous or sublingual routes (for certain inhalant allergens) are approved in the United States. In children, immunotherapy has been shown to prevent the progression of allergic rhinitis to asthma and may prevent sensitization to new allergens in monosensitized individuals.

Berings M, Karaaslan C, Altunbulakli C, et al. Advances and highlights in allergen immunotherapy: on the way to sustained clinical and immunological tolerance. *J Allergy Clin Immunol.* 2017;150(5):1250–1267.

13. How common is exercise-induced bronchoconstriction (EIB) in children with allergic rhinitis?

Exercise is a trigger of bronchoconstriction in **40% to 50% of children** with allergic rhinitis compared with 90% of those diagnosed with asthma and 10% of those not known to have asthma or respiratory allergies. *EIB* (also known as *exercise-induced bronchospasm*) is defined as a 10% drop in FEV_1 from the value before exercise.

Randolph C. Exercise-induced bronchospasm in children. *Clinic Rev Allerg Immunol.* 2008;34(2):205–216.

ASTHMA

14. What are the major determinants of asthma?

- **Innate immunity**: intrinsic tendency of individual immune system to respond in a certain pattern; specifically to produce Th2 cytokines rather than Th1 in response to a given stimulus
- **Genetics**: asthma has a heritable component, but the genetics are complex; although several loci have been implicated, none account for a substantial proportion of disease
- **Environmental**: two major factors have been identified in the development and persistence of asthma: aeroallergens (particularly sensitization and exposure to dust mites and *Alternaria* mold) and viral infections (e.g., respiratory syncytial virus [RSV], rhinovirus). Other, less well-established environmental influences in the development of asthma include tobacco smoke, air pollution, and obesity.

National Asthma Education and Prevention Program: Expert Panel Report III. Guidelines for the diagnosis and management of asthma. www.nhlbi.nih.gov. Accessed June 20, 2019.

15. When does asthma usually have its onset of symptoms?

About 50% of childhood asthma develops before the age of 3 years, and nearly all has developed by the age of 7 years. The signs and symptoms of asthma, including chronic cough, may be evident much earlier than the actual diagnosis, but may be erroneously attributed to recurrent pneumonia.

American Lung Association. www.lungusa.org. Accessed May 19, 2019.

16. Which children with wheezing at an early age are likely to develop chronic asthma?

Although about one-third of children will have an episode of wheezing before they are 1 year of age, most (80%) do not develop persistent wheezing after age 3 years. Risks factors for persistence include the following:

- Positive family history of asthma (especially maternal)
- Increased IgE levels
- Atopic dermatitis
- Rhinitis not associated with colds
- Secondhand smoke exposure

Taussig LM, Wright AL, Holberg CJ, et al. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol.* 2003;111(4):661–675.

17. What historical points are suggestive of an allergic basis for asthma?

- Seasonal nature with concurrent rhinitis (suggesting pollen)
- Symptoms worsen when visiting a family with pets (suggesting animal dander)
- Wheezing occurs when carpets are vacuumed or bed is made (suggesting mites)
- Symptoms develop in damp basements or barns (suggesting molds)

18. What are other potential triggers for asthma?

- Upper airway infections (rhinitis, sinusitis)
- Cold air
- Weather changes
- Exercise
- Environmental (pollutants, cigarette smoke)
- Irritants (strong odors, paint fumes, chlorine)
- Emotional extremes (stress, fear, crying, laughing)
- Medications (nonsteroidal anti-inflammatory drugs, aspirin, beta blockers)
- Foods, food additives
- Gastroesophageal reflux disease
- Hormonal (menstrual, premenstrual)

American Academy of Allergy, Asthma and Immunology. www.aaaai.org. Accessed March 11, 2020.

19. What is the time course of EIB?

EIB is condition in which there is an acute onset of bronchoconstriction that typically occurs after (sometimes during) exercise. Five percent to 20% of the general population may have EIB compared with up to 90% of those diagnosed with symptomatic persistent asthma. Symptoms are most commonly cough (although these can include wheezing, chest tightness, and unusual shortness of breath or excess mucus) with a peak 5 to 10 minutes after the conclusion of exercise and with resolution within 30 to 60 minutes.

Weiler JM, Brannan JD, Randolph CC, et al. Exercise-induced bronchoconstriction update—2016. *J Allergy Clin Immunol.* 2016; 138(5):1292–1295.e36.

20. How is EIB diagnosed?

Exercise challenge is the preferred method. EIB is likely if the peak flow rate or FEV$_1$ drops by 10% after 6 minutes of vigorous exercise, either in a laboratory or field setting. This exercise can include jogging on a motor-driven treadmill (15% grade at 3 to 4 mph), riding a stationary bicycle, or running up and down a hallway or around a track in field testing. The greatest reduction in FEV$_1$ is usually seen 5 to 10 minutes after exercise. As further verification of the diagnosis, if the patient has developed a decreased peak flow (and possibly wheezing), two puffs of a beta-2 agonist should be administered to attempt to reverse the bronchospasm.

Aggarwal B, Mulgirigama A, Berend N. Exercise-induced bronchoconstriction: prevalence, pathophysiology, patient impact, diagnosis and management. *NPJ Prim Care Respir Med.* 2018;28(1):31.

21. What is the likely mechanism that causes EIB?

The leading theory is an **osmotic** one. Increased ventilation during the hyperventilation of exercise (especially in dry air) causes water loss from airway surfaces through evaporation. This reduction in epithelial liquid volume causes osmotic changes, which in turn lead to mast cell degranulation. Mast cells release prostaglandins (especially prostaglandin D2), leukotrienes, histamine, and tryptase. Many of these are signaling molecules, which mediate airway smooth muscle contraction and increase mucus production, microvascular permeability, and sensory nerve activation. The release of these mast cell components, initially generated by osmotic changes, are thought to be the main stimulus for bronchoconstriction and airway edema.

Aggarwal B, Mulgirigama A, Berend N. Exercise-induced bronchoconstriction: prevalence, pathophysiology, patient impact, diagnosis and management. *NPJ Prim Care Respir Med.* 2018;28(1):31.

Weiler JM, Brannan JD, Randolph CC, et al. Exercise-induced bronchoconstriction update—2016. *J Allergy Clin Immunol.* 2016; 138(5):1292–1295.e36.

22. What are other bronchoprovocation tests for assessing airway reactivity?

- **Eucapnic voluntary hyperventilation (EVH)** involves breathing a dry gas at an increased respiratory rate in an effort to induce bronchospasm and a decrease of FEV_1 of $>10\%$.
- **Pharmacologic challenge** by inhalation of agents that act on smooth muscle (e.g., methacholine or histamine) or osmotic provocation (mannitol). The threshold concentration required to induce bronchospasm (decline in FEV_1 by 20%) is determined and compared with that required in healthy controls.
- **Antigen challenge** can be used for specific identification of a suspected allergen or occupational trigger. This is done only at specialized centers and may require prolonged observation ($>$24 hr) to identify and potentially treat a late-phase response.
- **Aspirin challenge** is performed in patients with suspected aspirin-exacerbated respiratory disease (AERD) who have a medical indication for treatment with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).

Leuppi JD. Bronchoprovocation tests in asthma: direct versus indirect challenges. *Curr Opin Pulm Med.* 2014;20(1):31–36.

Boulet LP, Gauvreau G, Boulay ME, et al. The allergen bronchoprovocation model: an important tool for the investigation of new asthma anti-inflammatory therapies. *Allergy.* 2007;62(10):1101–1110.

23. A 15-year-old with repeated shortness of breath after track practice has suspected EIB, but pulmonary function tests are normal, bronchoprovocation testing is negative, and he has no response to treatment with asthma medications. What is a likely alternative?

Exercise-induced laryngeal obstruction (EILO). This group of diagnoses includes *vocal cord dysfunction* and *exercise-induced laryngomalacia*. In the former, during exercise, the vocal cords adduct during inspiration to cause shortness of breath, chest tightness, cough, or stridor. In the latter, there is inspiratory prolapse of supraglottic structures, which causes dyspnea and/or stridor. In both cases, there is paradoxical laryngeal motion—narrowing occurs when a bigger breath is taken. The precise reasons are unclear but may be related to smaller airway dimensions, inhibition of laryngeal reflexes, or impaired innervation and/or power of the laryngeal muscles. The gold-standard test for diagnosis is flexible nasoendoscopy with continuous video recording of the larynx throughout exercise.

Nordang L, Norlander K, Walsted ES. Exercise-induced laryngeal obstruction—an overview. *Immunol Allergy Clin North Am.* 2018; 38(2):271-280.

24. What mechanisms lead to airway obstruction during an acute asthma attack?

The main causes of airflow obstruction in acute asthma are **airway inflammation**, including **edema**, **bronchospasm**, and **increased mucus production**. Chronic inflammation may eventually result in airway remodeling, which may not be clinically apparent without pulmonary function testing.

Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet.* 2018;391(10122):783–800.

25. All that wheezes is not asthma. What are other noninfectious causes?

- **Aspiration pneumonitis:** especially in a neurologically impaired infant or an infant with gastroesophageal reflux, and especially if there is coughing, choking, or gagging with feedings. If there is a clear association with feedings, consider the possibility of a tracheoesophageal fistula.
- **Bronchiolitis obliterans:** chronic wheezing often after infection (e.g., *Mycoplasma* or viral illnesses, especially adenovirus)
- **Bronchopulmonary dysplasia:** especially if there has been prolonged oxygen therapy or a ventilatory requirement during the neonatal period
- **Ciliary dyskinesia:** especially if recurrent otitis media, sinusitis, or situs inversus is present
- **Congenital malformations:** including tracheobronchial anomalies, tracheomalacia, lung cysts, and mediastinal lesions

- **Cystic fibrosis (CF):** if wheezing is recurrent and associated with failure to thrive, chronic diarrhea, or recurrent respiratory infections
- **Congenital cardiac anomalies:** especially lesions with large left-to-right shunts
- **Foreign-body aspiration:** if associated with an acute choking episode in an infant >6 months
- **Vascular rings, slings, or airway compression**

26. How is the severity of an acute asthma attack estimated?

See Table 16.1.

Table 16.1 Classifying Severity of Asthma Exacerbations in the Urgent or Emergency Care Setting

	SYMPTOMS AND SIGNS	INITIAL PEF (OR FEV$_1$)	CLINICAL COURSE
Mild	Dyspnea only with activity (assess tachypnea in young children)	PEF $\geq$70% predicted or personal best	• Usually cared for at home • Prompt relief with inhaled SABA • Possible short course of oral systemic corticosteroids
Moderate	Dyspnea interferes with or limits usual activity	PEF 40%-69% predicted or personal best	• Usually requires office or ED visit • Relief from frequent inhaled SABA • Oral systemic corticosteroids; some symptoms last for 1-2 days after treatment is begun
Severe	Dyspnea at rest; interferes with conversation	PEF <40% predicted or personal best	• Usually requires ED visit and likely hospitalization • Partial relief from frequent inhaled SABA • Oral systemic corticosteroids; some symptoms last for >3 days after treatment is begun • Adjunctive therapies are helpful
Subset: Life threatening	Too dyspneic to speak; perspiring	PEF <25% predicted or personal best	• Requires ED/hospitalization; possible ICU • Minimal or no relief from frequent inhaled SABA • Intravenous corticosteroids • Adjunctive therapies are helpful

ED, Emergency department; *FEV$_1$*, forced expiratory volume in 1 second; *ICU*, intensive care unit; *PEF*, peak expiratory flow; *SABA*, short-acting beta-2 agonist.

Adapted from the National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051).

27. Is a chest radiograph necessary for all children who wheeze for the first time?

A chest radiograph should be considered for a first-time wheezing patient in the following situations:

- Findings on physical examination that may suggest other diagnoses
- Marked asymmetry of breath sounds (suggesting a foreign-body aspiration)
- Suspected pneumonia
- History suggestive of foreign-body aspiration
- Hypoxemia or marked respiratory distress
- Older child with no family history of asthma or atopy
- Suspected congestive heart failure (CHF)
- History of trauma that may have caused injury to the airway (e.g., burns, scalds, blunt or penetrating injury)

28. What are the usual findings on arterial blood gas sampling during acute asthma attacks?

The most common finding is **hypocapnia** (i.e., low $PaCO_2$) because hypoxemia intensifies respiratory drive, resulting in hyperventilation (unless the child is being treated with oxygen). *Hypercapnia* is a serious sign that suggests the child is nearing respiratory failure. This finding should prompt consideration of ventilatory support by noninvasive means (bilevel positive airway pressure [BiPAP]) or endotracheal intubation and mechanical ventilation.

29. What are the indications for hospital admission in children with asthma?

After therapy in the emergency department, admission is advisable if a child has any of the following:

- Depressed level of consciousness
- Incomplete response with moderate retractions and/or wheezing, peak flow of <50% predicted, pulsus paradoxus of >15 mm Hg, SaO_2 of $\leq$90%, $PaCO_2$ $\geq$42 mm Hg

- Breath sounds diminished significantly
- Evidence of dehydration
- Pneumothorax
- Residual symptoms and history of severe attacks involving prolonged hospitalization (especially if intubation was required)
- Parental unreliability

An equally difficult (and very unpredictable) challenge relates to predicting which patients will relapse after responding to therapy and subsequently require hospitalization. This is a major problem because rates of relapse in asthma can approach 20% to 30%.

30. What are the possible acute side effects of albuterol and other beta agonists?

- **General:** hypoxemia, tachyphylaxis
- **Renal:** hypokalemia
- **Cardiovascular:** tachycardia, palpitations, premature ventricular contractions, atrial fibrillation
- **Neurologic:** headache, irritability, insomnia, tremor, weakness
- **Gastrointestinal:** nausea, heartburn, vomiting

31. What is the role of magnesium sulfate in acute asthma attacks?

Magnesium sulfate is a known smooth muscle relaxant most commonly used in the treatment of preeclampsia. In asthmatic patients, when used in conjunction with standard bronchodilators and corticosteroids, intravenous magnesium sulfate can provide additional bronchodilation, with a reduced likelihood of hospital admission. It is most commonly used when severely ill patients have failed to respond to conventional therapy. Inhaled magnesium sulfate as an adjuvant therapy in children is currently under study. Adult studies have demonstrated significant improvements in respiratory function and lower hospital admission rates.

Su Z, Li R, Gai Z. Intravenous and nebulized magnesium sulfate for treating acute asthma in children: a systematic review and meta-analysis. *Ped Emerg Care.* 2018;34(6):390–395.

Knightly R, Milan SJ, Hughes R, et al. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev.* 2017;11: CD003898.

32. How is chronic asthma severity classified among children 5 to 11 years of age?

The National Heart, Lung, and Blood Institute and National Asthma Education and Prevention Program (NAEPP) define severity in terms of impairment and risk. Four categories are listed: **intermittent**, **mild persistent**, **moderate persistent**, and **severe persistent**. Categorization, which is also separately done for 0 to 4 years and ≥12 years, helps guide therapy (Table 16.2).

National Asthma Education and Prevention Program Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma. Full Report 2007*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007: NHLBI publication 08–4051.

33. What is the first-line pharmacologic treatment for patients with *persistent* asthma?

Inhaled corticosteroids. Daily administration significantly improves symptoms, reduces exacerbations, and allows healing of the chronic inflammatory changes that have taken place in the airways over time. Dosing and the use of adjunctive medications (e.g., long-acting inhaled beta-2 agonists, leukotriene-receptor antagonists) depend on frequency and severity of symptoms and exacerbations.

Ramadan AA, Gaffin JM, Israel E, Phipatanakul W. Asthma and corticosteroid responses in childhood and adult asthma. *Clin Chest Med.* 2019;40(1):163–177.

34. What are the four main components of optimal asthma care?

According to the NAEPP, optimal asthma care should cover all of the following domains:

- Assessment and monitoring of symptoms
- Education
- Control of environmental factors and comorbidities
- Review and adjustment of medications

National Asthma Education and Prevention Program. Expert Panel Report III: guidelines for the diagnosis and management of asthma. www.nhlbi.nih.gov. Accessed June 19, 2019.

35. Do inhaled steroids affect growth in children?

Results are conflicting but tend to indicate that mild growth suppression occurs among children receiving moderate to high doses, particularly in children with more severe asthma and primarily during the first year of therapy (about 1 cm).

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Table 16.2 Classifying Asthma Severity and Initiating Therapy in Children

		Classifying Asthma Severity and Initiating Therapy in Children							
			Persistent						
COMPONENTS OF SEVERITY		***Intermittent***		***Mild***		***Moderate***		***Severe***	
		AGES 0-4	**AGES 5-11**	**AGES 0-4**	**AGES 5-11**	**AGES 0-4**	**AGES 5-11**	**AGES 0-4**	**AGES 5-11**
Impairment	Symptoms	≤2 days/week		>2 days/week but not daily		Daily		Throughout the day	
	Nighttime awakenings	0	≤2 ×/month	1-2 ×/month	3-4 ×/month	3-4 ×/month	>1 ×/week but not nightly	>1 ×/week	Often 7×/week
	Short-acting beta-2 agonist use for symptom control	≤2 days/week		>2 days/week but not daily		Daily		Several times per day	
	Interference with normal activity	None		Minor limitation		Some limitation		Extremely limited	
	Lung function	N/A	Normal FEV$_1$ between exacerbations	N/A	>80% >80%	N/A	60%-80% 75%-80%	N/A	<60% <75%
	• FEV$_1$ (predicted) or peak flow (personal best)		>80%						
	• FEV$_1$/FVC		>85%						
Risk	Exacerbations requiring oral systemic corticosteroids (consider severity and interval since last exacerbation)	0-1/year		≥2 exacerbations in 6 months requiring oral synthetic corticosteroids or ≥4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma.	→ ≥2 ×/year (see notes) Relative annual risk may be related to Fev$_1$ →				

FEV$_1$, Forced expiratory volume in 1 second; *FVC,* forced expiratory capacity; *ICS,* inhaled corticosteroids; *ICU,* intensive care unit; *N/A,* not applicable.

Adapted from the National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051).

The reduction in growth is generally not progressive. It is important that children who require the extended use of inhaled steroids are monitored for height and height velocity and for cataracts.

Wolfgram PM, Allen DB. Effects of inhaled corticosteroids on growth, bone metabolism, and adrenal function. *Adv Pediatr.* 2017; 64(1):331–345.
Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. *Cochrane Database Sys Rev.* 2014;7:CD009471.
Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med.* 2012;367(10):904–912.

36. What is anti-IgE treatment for asthma?

Omalizumab is a humanized monoclonal anti-IgE antibody approved for adjunctive therapy of severe persistent asthma in patients aged 6 years and older with an elevated total IgE and sensitivity to perennial allergens. It prevents free serum IgE from binding to its high-affinity receptors on mast cells and basophils. Omalizumab has been shown to reduce asthma exacerbations. It should be considered as an add-on for children >6 years of age who have inadequately controlled, severe, persistent allergic IgE-mediated asthma who require continuous or frequent oral corticosteroids. Rarely, symptoms of anaphylaxis may develop up to 24 hours after administration, so the clinician administering the drug should be prepared to treat anaphylaxis, and the patient should carry self-injectable epinephrine for 1 day after administration.

Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc.* 2017;38(4):250-263.
Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev.* 2014;1:CD003559.

37. Is there a role for complementary and alternative medicines in the treatment of asthma?

There are no clear directions or guidelines for the use of complementary and alternative medicines for children with asthma, although these therapies are often independently used by families. Hypnosis, yoga, relaxation techniques, acupuncture, and massage have shown benefit in some studies, but a review of studies involving mind–body techniques, relaxation, manual therapies, and diet has found a tendency to little or no significant difference between sham (placebo) and active therapy.

Ricklefs I, Hohmann-Ebbers M, Herz A, Kopp MV. Use of complementary and alternative medicine in children with asthma. *Pediatr Allergy Immunol.* 2018;29(3):326–328.
Snyder J, Brown P. Complementary and alternative medicine in children: an analysis of the recent literature. *Curr Opin Pediatr.* 2012;24:539–546.

38. Is a nebulizer more effective than a metered-dose inhaler (MDI) with a spacer for the treatment of asthma?

For the treatment of exacerbations of asthma, nebulizers are primarily used in children <2 years of age because of the ease of administration. Although an MDI with a spacer is used more commonly among older children, several studies in emergency rooms indicate that they are equally or more effective than nebulizers among young children, even those with moderate or severe acute asthma. Furthermore, the MDI with a spacer requires less treatment time, has fewer side effects, and often preferred by patients and parents. Children <5 years typically require a facemask attached to the MDI/spacer device.

Smith C, Goldman RD. Nebulizers versus pressurized metered-dose inhalers in preschool children with wheezing. *Can Fam Physician.* 2012;58(5):528–530.
Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. *J Pediatr.* 2004; 145(2):776–779.

39. How useful are pulmonary function tests when evaluating and following children with asthma?

Spirometry is used for both the diagnosis and monitoring of asthma in children ≥ 5 years of age. The diagnosis of asthma requires airflow obstruction with at least a 12% improvement, or reversibility, in FEV_1 from baseline with the inhalation of a short-acting beta agonist. Patient history and physical examination do not adequately predict the degree of a patient's airflow obstruction. Spirometry is also used to monitor asthma after diagnosis and treatment. The goals of asthma therapy include normal or near-normal lung function with treatment. Spirometry should be performed on the patient after treatment has been initiated or changed, based on abnormal lung function, to assess improvement. It should also be performed during periods of prolonged loss of asthma control. Otherwise, in symptomatically controlled patients, it should be repeated at least yearly to monitor the patient long term. *Handheld peak flow* measurements are useful for monitoring patients, but not for initial diagnosis.

National Asthma Education and Prevention Program. Expert Panel Report III: guidelines for the diagnosis and management of asthma. www.nhlbi.nih.gov. Accessed June 19, 2019.

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40. What proportion of children with asthma “outgrow” their symptoms?

Popular pediatric teaching has been that most children with asthma outgrow their symptoms. However, studies suggest that this is erroneous, and that only 30% to 50% become free of symptoms, primarily those with milder disease. Many children who appear to outgrow symptoms have recurrences during adulthood. Studies also indicate that many infants who wheeze with viral infections and are asymptomatic between illnesses tend to outgrow their asthma. Children with (1) early-onset asthma (age <3 years) with a positive parental history for asthma, (2) atopic dermatitis, or (3) sensitization to aeroallergens are more likely to have persistent or recurrent bronchospasm. Although the overall trend is for asthma to become milder, a large percentage of adults have persistent obstructive disease, both recognized and unrecognized.

Link HW. Pediatric asthma in a nutshell. *Pediatr Rev.* 2014;35(7):287–297.

Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med.* 2003;349(15):1414–1422.

41. What diagnosis should be considered in a patient with poorly controlled asthma with recurrent infiltrates who has central bronchiectasis on a chest computed tomography (CT) scan along with peripheral blood eosinophilia?

Allergic bronchopulmonary aspergillosis. This is a T-cell–mediated hypersensitivity response to *Aspergillus fumigatus* (a ubiquitous fungus) that can cause migrating pulmonary infiltrates and central bronchiectasis. The condition occurs as a complication primarily in patients with asthma and CF. Diagnosis relies on an abnormal chest radiograph and CT scan, skin prick reactivity to *A. fumigatus*, elevated total serum IgE >417 IU/L, and positive serum antibodies to *A. fumigatus* (IgE and/or IgG).

Agarwal R, Sehgal IS, Dhooria S, Aggarwal AN. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Expert Rev Respir Med.* 2016;10(12):1317–1334.

Greenberger PA, Bush RK, Demain JG, et al. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract.* 2014;2(6):703–708.

KEY POINTS: ASTHMA

1. Asthma is characterized by recurrent reversible airway obstruction and inflammation, often with identifiable triggers.
2. Typical abnormalities on spirometry include the following: decreased FEV_1 and FEV_1/FVC ratio; increase in FEV_1 ($>12\%$) with bronchodilator.
3. Classification is based on frequency of symptoms and exacerbations; nighttime awakenings; limitation of normal activities; use of oral steroids; and lung function—intermittent, mild persistent, moderate persistent, and severe persistent.
4. Pa_{CO_2} measurements that are normal (40 mm Hg) or rising in an asthmatic patient with tachypnea, or significant respiratory distress, are worrisome for evolving respiratory failure.
5. Signs of impending respiratory failure include severe retractions, accessory muscle use (especially sternocleidomastoids), decreased muscle tone, and altered mental status.

BRONCHIOLITIS

42. What are the typical features of bronchiolitis?

Bronchiolitis is a clinical diagnosis, identifying a syndrome that occurs in children under 2 years of age, characterized by upper respiratory symptoms (rhinorrhea), usually with fever, followed by lower respiratory tract signs (tachypnea, wheezing, crackles). This is typically caused by infection with a viral pathogen. In young children, the presentation may overlap with recurrent virus-induced wheezing and asthma.

43. What are the most common causes of bronchiolitis?

Respiratory syncytial virus (RSV) is estimated to cause 50% to 80% of cases of bronchiolitis in children. Up to 100,000 children are hospitalized annually in the United States as a result of this pneumovirus, which is different from—but closely related to—the paramyxoviruses. Disease most commonly occurs during outbreaks in winter or spring in the United States and during the winter months of July and August in the Southern Hemisphere. In the first 2 years of life, 90% of children will become infected with RSV and up to 40% will develop some lower respiratory disease. Other agents responsible for bronchiolitis include human metapneumovirus (second most common cause), parainfluenza virus, influenza virus types A and B, adenovirus, rhinovirus, and coronavirus.

Teshome G, Gattu R, Brown R. Acute bronchiolitis. *Pediatr Clin North Am.* 2013;60(5):1019–1034.

Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med.* 2009;360(6):588–598.

44. What are the predictors of severe bronchiolitis?

The single best predictor at an initial assessment appears to be **oxygen saturation**, which can be determined by pulse oximetry. An Sao_2 of $<95\%$ correlates with more severe disease; a low Sao_2 is often not clinically apparent, and objective measurements are necessary. An arterial blood gas with a $\mathrm{Pao}_2 \leq 65$ mm Hg or a Paco_2 of >40 mm Hg is particularly worrisome. Other predictors of increased severity include the following:

- An ill or "toxic" appearance
- History of prematurity (gestational age <34 weeks)
- Atelectasis on chest radiograph
- Respiratory rate of >60 breaths per minute
- Infant <3 months old
- Presentation with apnea

45. What are the typical findings on a chest radiograph in a child with bronchiolitis?

The picture is **varied**. Most commonly, there is hyperinflation of the lungs. About 25% of hospitalized infants have atelectasis or infiltrates. Bilateral interstitial abnormalities with peribronchial thickening are common, or patients may have lobar, segmental, or subsegmental consolidation that can mimic bacterial pneumonia. Bacteremia or secondary bacterial pneumonia, however, is unusual in patients with bronchiolitis. With the possible exception of atelectasis, the chest radiograph findings do not correlate well with the severity of the disease. American Academy of Pediatrics (AAP) clinical practice guidelines recommend against routine chest x-rays for evaluation of infants presenting with classic features of bronchiolitis, as unnecessary chest x-rays contribute to health care costs, radiation exposure, and antibiotic overuse and provide no clinical benefit. However, radiography in the evaluation of bronchiolitis continues to be overused.

Burstein B, Plint AC, Papenburg J. Use of radiography in patients diagnosed as having acute bronchiolitis in US emergency departments, 2007-2015. *JAMA.* 2018;320(15):1598–1600.

Ralston SL, Lieberthal AS, Meissner HC, et al. AAP clinical practice guideline: the diagnosis, management and prevention of bronchiolitis. *Pediatrics.* 2014;134(5):e1474–e1502.

46. Which patients with bronchiolitis are at risk for apnea?

Apnea in patients hospitalized with bronchiolitis has ranged from 3% to 7% in studies. Concerns of apnea are often used as a rationale for hospitalization. In one study, higher-risk patients were those born at term and age <1 month, preterm infants (<37 weeks of gestation) and <48 weeks postconception, and those with an observed apneic episode before evaluation. If none of these clinical criteria were present, the risk for apnea was $<1\%$. In another study, independent predictors of apnea were age <2 weeks, birth weight <2.3 kg, reported apneic event during current illness, and preadmission oxygen saturation $<90\%$.

Walsh P, Cunningham P, Merchant S, et al. Derivation of clinical decision rules to identify infants at risk for central apnea. *Pediatrics.* 2015;136(5):e1228–1236.

Schroeder AR, Mansbach JM, Stevenson M, et al. Apnea in children hospitalized with bronchiolitis. *Pediatrics.* 2013;132(5):e1194-e1201.

Willwerth BM, Harper MB, Greenes DS. Identifying hospitalized infants who have bronchiolitis and are at high risk for apnea. *Ann Emerg Med.* 2006;48(4):4441–4447.

47. What therapies are effective for bronchiolitis?

Treatment for bronchiolitis is primarily supportive, and for mild to moderate cases managed at home, no specific therapy is indicated. For more severe cases requiring hospitalization, supplemental oxygen should be given as needed to maintain $\mathrm{Sao}_2 >90\%$. Use of high-flow nasal cannula and continuous positive airway pressure (CPAP) may be effective at preventing respiratory failure and intubation in more severe cases. Helium/oxygen mixtures (heliox) appear to offer some benefit in the first hour after therapy initiation. Nasal suctioning is helpful for comfort, but frequent deep suctioning is not recommended because it may cause more trauma and irritation. Multiple other therapies have been deployed, including bronchodilators, inhaled racemic epinephrine, inhaled and systemic steroids, anticholinergics, montelukast, and antibiotics, but their routine use is not supported by evidence. Use of chest physiotherapy to mobilize secretions also does not improve outcomes. Results of the use of nebulized hypertonic saline have been conflicting.

Korppi M. Therapeutic strategies for pediatric bronchiolitis. *Expert Rev Respir Med.* 2019;13(1):95–103.

Jat KR, Mathew JL. Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. *Cochrane Database Syst Rev.* 2019;1:CD010473.

Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. *Lancet.* 2017;389(10065):211–224.

48. Is there a vaccine to prevent RSV infection?

No, there is not yet a safe and effective vaccine against RSV, although vaccines are in development. Palivizumab (Synagis), a monoclonal antibody directed against RSV, is effective for prophylaxis of RSV infection in high-risk infants.

It is given intramuscularly and must be given once per month during the RSV season. This drug is not indicated for the treatment of RSV infection.

Gerretsen HE, Sande CJ. Development of respiratory syncytial virus (RSV) vaccines for infants. *J Infect.* 2017;74(Suppl 1): S143–S146.

49. Does infection with RSV confer lifelong protection?

No. In fact, reinfection is very common. In day care centers, up to 70% of infants who acquire RSV infections during the first year of life are reinfected during the subsequent 2 years. Primary infections tend to be the most severe episodes, with subsequent illnesses being milder. In older children and adults, RSV infections present with the same symptoms as "colds," and reinfection is also common.

50. If a 5-month-old child is hospitalized as a result of RSV bronchiolitis, what should the parents be told about the likelihood of future episodes of wheezing?

In follow-up studies, 40% to 50% of these infants have subsequent recurrent episodes of wheezing, usually during the first year after illness. Subclinical pulmonary abnormalities may also persist. The question of whether the pulmonary sequelae are the result of the bronchiolitis or of a genetic predisposition to wheezing or asthma remains unclear. Factors such as pulmonary abnormalities before the illness, passive cigarette smoke exposure, atopic diathesis, and immunologic responses of virus-specific IgE determine the risk for recurrence.

KEY POINTS: BRONCHIOLITIS

1. The most common causes are RSV and metapneumovirus.
2. The illness severity is greatest between 2 and 6 months of age.
3. Atelectatic changes on chest radiograph are common.
4. In most cases, supportive care is all that is needed.
5. Although multiple therapeutic approaches in bronchiolitis have been studied, very few have been clearly found to provide clinical benefit.

CLINICAL ISSUES

51. What are the causes of hemoptysis?

Hemoptysis is the expectoration of blood from the lower respiratory tract. In children, the most common causes are **pulmonary infection**, **aspirated foreign body**, and **bronchiectasis** (usually in patients with CF). Less common are cardiac causes (CHF, pulmonary hypertension), rheumatologic disorders, tumors, and vascular malformations.

52. What are some mimics of hemoptysis?

Bleeding from the gastrointestinal tract *(hematemesis)* or the upper respiratory tract (nose, sinuses) may present as coughing up blood and may require visualization to determine the source. *Hematemesis* is typically acidic, dark red or brown, and preceded by vomiting/retching. *Hemoptysis* is usually alkaline, bright red and frothy, and accompanied by gurgling and cough. *Factitious bleeding* (e.g., biting tongue or deliberately presenting blood from other source as expectorated) has been reported on rare occasions.

53. What are the indications for surgical repair of pectus excavatum?

This remains an area of considerable controversy, despite the development of minimally invasive procedures (e.g., Nuss procedure). Nearly 1 in 400 children have this congenital chest wall anomaly, with males five times more frequently affected than females. Children with pectus excavatum (Fig. 16.2) may report symptoms of exercise intolerance, chest pain, shortness of breath, and psychosocial and body image problems. On physiologic testing they may have reduced total lung capacity, reduced vital capacity, increased residual volume, and reduced cardiac stroke volume during maximal exercise. However, most patients are still in the normal range for these values. Factors that contribute to the decision to have corrective surgery include:

- PSI >3.25 (**P**ectus **S**everity **I**ndex, or Haller index, is the ratio of the lateral diameter of the chest on CT to the distance between the sternum and spine at the point of maximal depression)
- Restrictive defect on pulmonary function testing
- Cardiac compression, displacement, mitral valve prolapse, murmurs, or conduction abnormalities
- Worsening deformity and physiologic symptoms
- Significant distress over appearance

Abdullah F, Harris J. Pectus excavatum: more than a matter of aesthetics. *Pediatr Ann.* 2016;45(11):e403–e406.

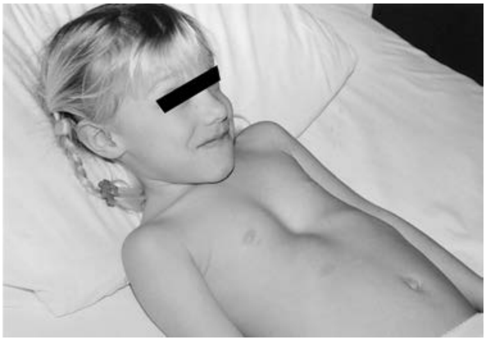

Fig. 16.2 Pectus excavatum. (From James EC, Corry RJ, Perry JF. *Principles of Basic Surgical Practice.* Philadelphia, PA: Hanley & Belfus; 1987:173.)

54. What is the optimal timing and outcome of pectus excavatum repair?

The consensus is to time a repair for **late childhood to mid-adolescence**. This allows for cartilage remodeling but minimizes the chance of recurrence after the pubertal growth spurt. After surgery there is reliable improvement in body image. Physiologic benefits on cardiopulmonary function are of much lesser magnitude and much more variable. The more severely affected tend to have more benefit.

Pilegaard H, Licht PB. Minimal repair of pectus excavatum and carinatum. *Thorac Surg Clin.* 2017;27(2):123–131.
Obermeyer RJ, Goretsky MJ. Chest wall deformities in pediatric surgery. *Surg Clin North Am.* 2012;92(3):669–684.

55. What are the most common causes of chronic cough?

The differential diagnosis of *chronic cough* (cough >4 weeks) is very long. Common causes include asthma (although typically manifesting not with cough alone), protracted bacterial bronchitis (a chronic *wet* cough), and chronic postnatal drip. Other causes include congenital anomalies, infectious or postinfectious cough, gastroesophageal reflux, aspiration, physical and chemical irritation, and psychogenic cough. After a thorough history and physical examination, evaluation with a chest radiograph and spirometry can also help establish the diagnosis.

Chang AB, Oppenheimer JJ, Weinberger M, et al. Etiologies of chronic cough in pediatric cohorts. *Chest.* 2017;152(3):607–617.
Acosta R, Bahna SL. Chronic cough in children. *Pediatr Ann.* 2014;43(8):e176–e183.

56. When should the diagnosis of habit cough be considered?

A *habit cough* (or *psychogenic cough*) should be considered in children with a persistent dry, honking, explosive daytime cough that disappears with sleep. It is often distressing to hear and is disruptive at school. It commonly starts after a upper respiratory infection (URI). Physical examination and laboratory work are normal, and conventional therapies are ineffective. A behavioral approach with training in how to reduce the cough is the preferred treatment, although in some cases, psychological intervention is required; hypnosis has also been employed successfully.

57. What medications are most effective for cold symptoms in children?

Multiple studies have failed to show benefit over placebo of any particular medication, including dextromethorphan, diphenhydramine, codeine, and echinacea. In addition, because the use of over-the-counter cold and cough products with antihistamines and decongestants has been implicated with many adverse events, a U.S. Food and Drug Administration advisory committee has recommended against their use in children <6 years of age. Many manufacturers have voluntarily removed such products intended for children <2 years of age. Supportive care with patience and self-resolution of symptoms (tincture of time) remain the mainstays of treatment.

Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. *Cochrane Database Syst Rev.* 2014;11:CD001831.
Isbister GK, Prior F, Kilham HA. Restricting cough and cold medicines in children. *J Paediatr Child Health.* 2012;48(2):91–98.

58. Which is more effective for cough in children: antihistamines, antitussives, mucolytics, decongestants, or honey?

Honey. A number of studies have demonstrated that honey is a safe and somewhat effective treatment for cough associated with URI in children >1 year of age. Honey should not be given to children <1 year of age because of the risk for botulism.

Oduwole O, Udoh EE, Oyo-Ita A, Meremikwu MM. Honey for acute cough in children. *Cochrane Database Syst Rev.* 2018;4:CD007094.

59. What constitutes passive cigarette smoke?

Passive cigarette smoke consists of both the smoker's exhalation (mainstream smoke, about 15% of total) and the more noxious sidestream (the unfiltered burning end of the cigarette, about 85% of total).

60. What are the possible risks of passive cigarette smoke exposure?

- Decreased fetal growth and persistent adverse effects on lung function across childhood from smoking in pregnancy
- Increased incidence of sudden infant death syndrome
- Increased incidence of acute and chronic middle ear effusions
- Increased frequency of upper and lower respiratory tract infections
- Appearance of wheeze illness at an earlier age with more frequent exacerbations
- Impaired lung function during childhood from secondhand smoke after birth

Longer-term issues of increased cancer rates and cardiovascular disease remain under study. In addition, if a parent smokes, a child is twice as likely to become a smoker.

U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General.* www.surgeongeneral.gov/library/reports/secondhandsmoke/fullreport.pdf. Accessed May 19, 2019.

61. How is clubbing diagnosed?

Digital clubbing is the presence of increased amounts of connective tissue under the base of the fingernail. This may be determined by the following:

- **Rock the nail** on its bed between the examiner's finger and thumb. In patients with clubbing, the nail seems to be floating.
- **Visual inspection** reveals that the distal phalangeal depth (DPD), which is the distance from the top of the base of the nail to the finger pad, exceeds the interphalangeal depth (IPD), which is the distance from the top of the distal phalangeal joint to the underside of the joint. Normally, the DPD/IPD ratio is <1, but in patients with clubbing, it is >1.
- **The diamond (or Schamroth) sign:** Normally, if the nails of both index fingers or any other two identical fingers are opposed, there is a diamond-shaped window present between the nail bases (Fig. 16.3); this window disappears in patients with clubbing.

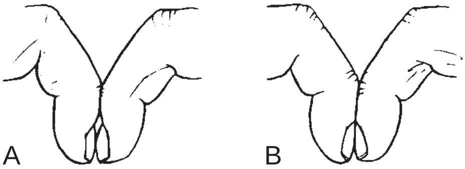

Fig. 16.3 Diamond sign of clubbing. (A) Normal child with a diamond-shaped window between the nail bases when the fingers are opposed. (B) In digital clubbing, the diamond-shaped window is obliterated by the increased amount of soft tissue under the base of the nail.

62. What are the causes of digital clubbing?

- **Pulmonary:** bronchiectasis (as in CF, bronchiolitis obliterans, ciliary dyskinesia), pulmonary abscess, empyema, interstitial fibrosis, malignancy (bronchial carcinoma), pulmonary atrioventricular fistula
- **Cardiac:** cyanotic congenital heart disease, chronic CHF, subacute bacterial endocarditis
- **Hepatic:** biliary cirrhosis, biliary atresia, α_1-antitrypsin deficiency
- **Gastrointestinal:** Crohn disease, ulcerative colitis, chronic amebic and bacillary diarrhea, polyposis coli, small bowel lymphoma
- **Endocrine:** thyrotoxicosis, thyroid deficiency
- **Hematologic:** thalassemia, congenital methemoglobinemia (rare)
- **Idiopathic:** may be a variation of normal and not indicative of underlying disease
- **Hereditary:** may be a variation of normal and not indicative of underlying disease

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Modified from Hilman BC. Clinical assessment of pulmonary disease in infants and children. In Hilman BC, ed. *Pediatric Respiratory Disease*. Philadelphia, PA: W.B. Saunders; 1993:61.

63. What conditions are associated with nasal polyps?

- *Children:* Nasal polyps are rare in children except as a manifestation of CF (Fig. 16.4). About 3% of children with CF have nasal polyps, which are often a recurrent problem that becomes more frequent with increasing age. For this reason, a child with nasal polyps should be referred for sweat testing to check for CF.
- *Adolescents:* There is a wider range of possible diagnoses, including CF, allergic rhinitis, chronic sinusitis, malignancy, "triad asthma" (asthma, nasal polyps, aspirin sensitivity), and ciliary dyskinesia syndrome (e.g., Kartagener syndrome).

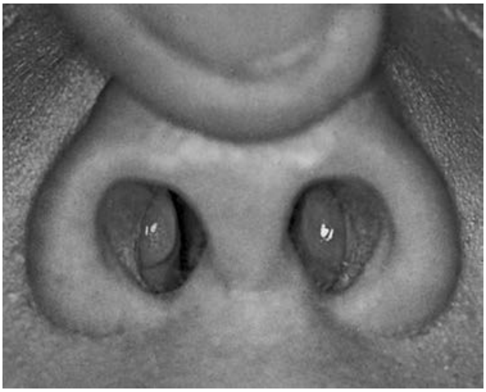

Fig. 16.4 Nasal polyps in a patient with cystic fibrosis. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis.* 4th ed. St. Louis, MO: Mosby; 2002:550.)

64. A patient with chronic sinusitis and recurrent pulmonary infections has a chest radiograph that demonstrates a right-sided cardiac silhouette. What diagnostic tests should be considered next?

Genetic testing or **electron microscopic examination** of cilia in bronchial or nasal turbinate biopsy. Findings are concerning for *primary ciliary dyskinesia (PCD)* or *immotile-cilia syndrome*. The presenting symptoms are a constellation of recurrent pulmonary infections, chronic sinusitis, recurrent otitis media, situs inversus, and infertility (in males). Structural ciliary abnormalities (most common are absent dynein arms) result in abnormal ciliary function and decreased clearance of respiratory secretions, thereby predisposing the patient to infection. In addition, because spermatozoa have tails with the same ultrastructural abnormalities as respiratory cilia, they move less well, causing infertility. The cause of the situs inversus (Fig. 16.5) is not fully understood, but it occurs in about 50% of individuals with PCD. It has been suggested that cilia are important for proper organ orientation during embryonic development and that dysfunctional cilia make organ orientation a random event, leading to situs inversus 50% of the time. PCD is inherited as an autosomal recessive disease with >30 mutational variants described.

Knowles MR, Zariwala M, Leigh M. Primary ciliary dyskinesia. *Clin Chest Med.* 2016;37(3):449–461.

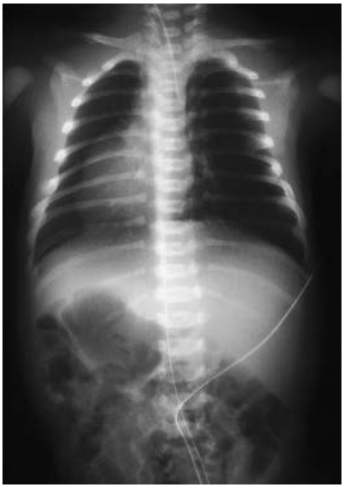

Fig. 16.5 Dextrocardia with situs inversus. (From Clark DA. *Atlas of Neonatology.* Philadelphia, PA: W.B. Saunders; 2000:115.)

65. What percentage of children snore?

Between 5% and 10% of preadolescent children are reported by their parents to snore at night.

66. What are common symptoms of obstructive sleep apnea (OSA) in children?

During sleep:

- Snoring (usually loud with obvious mouth breathing)
- Gasping, pauses (apnea), sometimes associated with coughing, choking, or snorting
- Restless sleep
- Nocturesis
- Nighttime sweating
- Parasomnias (e.g., sleep walking, night terrors)

Daytime:

- Headaches (usually morning)
- Hyperactivity, other behavioral problems (e.g., aggression)
- Tiredness, sleepiness (e.g., inappropriate napping)
- Poor school performance (e.g., inattention, learning problems)

Ehsan Z, Ishman SL. Pediatric obstructive sleep apnea. *Otolaryngol Clin North Am.* 2016;49(6):1449–1464.

Perkins J. Pediatric obstructive sleep apnea. In Richardson MA, Friedman NR, eds. *Clinician's Guide to Pediatric Sleep Disorders*. New York: Informa Healthcare; 2007:24.

67. What are the two major risk factors for OSA in children?

Adenotonsillar hypertrophy (the leading cause) and **obesity**. Other less common factors are craniofacial anomalies, neuromuscular disorders (e.g., cerebral palsy), and syndromic conditions (e.g., Down syndrome with anatomic abnormalities, hypotonia, and obesity).

68. What evaluations should be performed on a child with suspected OSA?

- **Physical examination** is used to assess for mouth breathing while awake, midface or mandibular hypoplasia, tonsillar hypertrophy, cleft palate, palatal deformity caused by adenoidal hypertrophy, failure to thrive, or obesity.
- **Overnight, attended polysomnography** in a pediatric sleep laboratory is the gold standard for the definitive diagnosis of OSA and can also help with risk stratification if surgical intervention is necessary (usually adenotonsillectomy).
- **Flexible nasopharyngoscopy** is useful for dynamic assessment of the nasal cavities, upper airway, and larynx.
- **Imaging** (by x-rays, CT, or magnetic resonance imaging [MRI]) is rarely helpful, except where there is abnormal craniofacial anatomy.
- **Cardiologic assessment** (electrocardiogram, echocardiography) is used for children with severe OSA to evaluate for signs of right heart strain or pulmonary hypertension, although both are much less common in children than in adults.

Ehsan Z, Ishman SL. Pediatric obstructive sleep apnea. *Otolaryngol Clin North Am.* 2016;49(6):1449-1464.

69. What are the potential long-term consequences of OSA?

The most severe complications of OSA in children are right ventricular hypertrophy, hypertension, polycythemia, respiratory acidosis with compensatory metabolic alkalosis, life-threatening cor pulmonale, and respiratory failure. Later in life, OSA is associated with an increased risk for cardiovascular morbidity and mortality. OSA is strongly implicated in the development of hypertension, ischemic heart disease, arrhythmias, and sudden death (in individuals with coexisting ischemic heart disease); it also contributes to the risk for stroke.

Capdevila OS, Kheirandish-Gozal L, Dayyat E, et al. Pediatric obstructive sleep apnea: complications, management, and long-term outcomes. *Proc Am Thorac Soc.* 2008;5(2):274–282.

70. What is the most common cause of infantile stridor?

Congenital laryngomalacia occurs as a result of prolapse of the poorly supported supraglottic structures—the arytenoids, the aryepiglottic folds, and the epiglottis—on inspiration (Fig. 16.6). Stridor is loudest in the supine position or with crying or agitation, but it typically does not interfere with feeding, sleep, or growth. There is an association with gastroesophageal reflux, but the direction of causality is unclear and may go both ways (i.e., more negative inspiratory pressures causing reflux, which causes further inflammation and swelling of the larynx). Symptoms usually resolve by the time the infant is 18 months old. More severe cases may need treatment with positive pressure (CPAP) or surgery (supraglottoplasty).

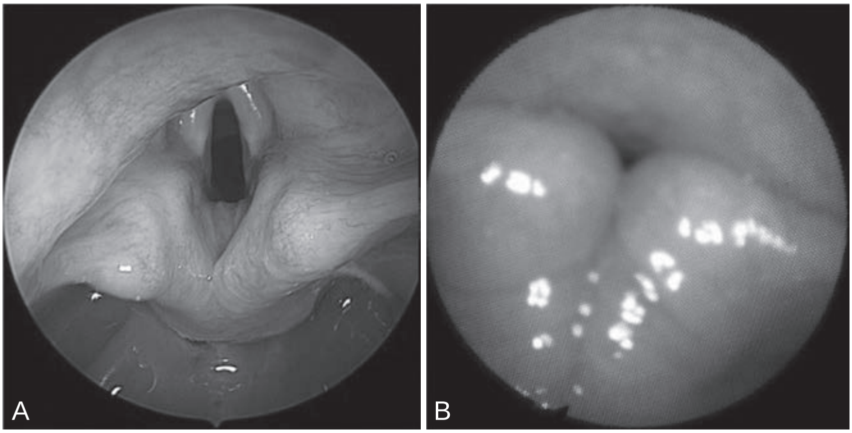

Fig. 16.6 Laryngomalacia. (A) Normal position of supraglottic structures during expiration. (B) Collapse of arytenoids during inspiration. (From Powitzky R, Stoner J, Fisher T, Digoy GP. Changes in sleep apnea after supraglottoplasty in infants with laryngomalacia. *Int J Pediatr Otolaryngol.* 2011;75:1234–1239.)

71. How can you clinically distinguish bilateral from unilateral vocal cord paralysis in an infant?

Normally, the vocal cords are tonically abducted, with voluntary adduction resulting in speech. With *unilateral paralysis,* one cord is ineffective for speech, and hoarseness results. The infant's cry may be weak or absent. Stridor is usually minimal but may be positional (e.g., sleeping on the side with the paralyzed cord up may allow it to fall to midline and produce obstructive sounds). With *bilateral paralysis,* hoarseness is less apparent and the cry remains weak, but stridor (both inspiratory and expiratory) is usually quite prominent; in addition, the infant is more likely to have frank symptoms of pulmonary aspiration.

72. What is the most common cause of chronic hoarseness in children?

Screamer nodes. These are vocal cord nodules caused by vocal abuse, such as repetitive screaming, yelling, and coughing. They are the cause of a hoarse voice in >50% of children when hoarseness persists for >2 weeks.

73. What are the most common symptoms and signs in children with suspected foreign-body aspiration?

Coughing and **choking** (witnessed or by history) occur in up to 80% to 90%, which highlights the importance of questioning about choking in a child who is evaluated for cough. The classic triad of *cough, wheeze,* and *unilaterally decreased breath sounds* is found in only about one-third to one-half of patients.

Tan HK, Brown K, McGill T. Airway foreign bodies: a 10-year review. *Int J Pediatr Otolaryngol.* 2000;56(2):91–99.

74. Which other clinical features are suggestive of foreign-body aspiration?

Symptoms and history
- Child <4 years
- Boys twice as common as girls
- Hemoptysis
- Respiratory infection not resolving with treatment
- Difficulty breathing

Signs
- Wheezing in a child who has no history of asthma
- Mediastinal shift
- Stridor

75. Are chest radiographs useful for evaluating a foreign-body aspiration?

Unfortunately, only about 10% to 20% of aspirated foreign bodies are radiopaque. Thus inspiratory films are often normal. Features suggesting a foreign-body aspiration are as follows:
- Expiratory chest radiograph showing asymmetry in lung aeration as a result of obstructive emphysema. The foreign body often acts as a ball-valve mechanism, allowing air in but not out (Fig. 16.7).
- Right and left lateral decubitus films that show the same asymmetry. These views are often used in uncooperative children who cannot or will not exhale on command.
- Local hyperinflation.
- Obstructive atelectasis.

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Because of its low sensitivity in detecting abnormalities, imaging has only an auxiliary role in evaluation for foreign-body aspiration. If there is sufficient clinical suspicion, the child should undergo bronchoscopy to definitively identify and remove a foreign body.

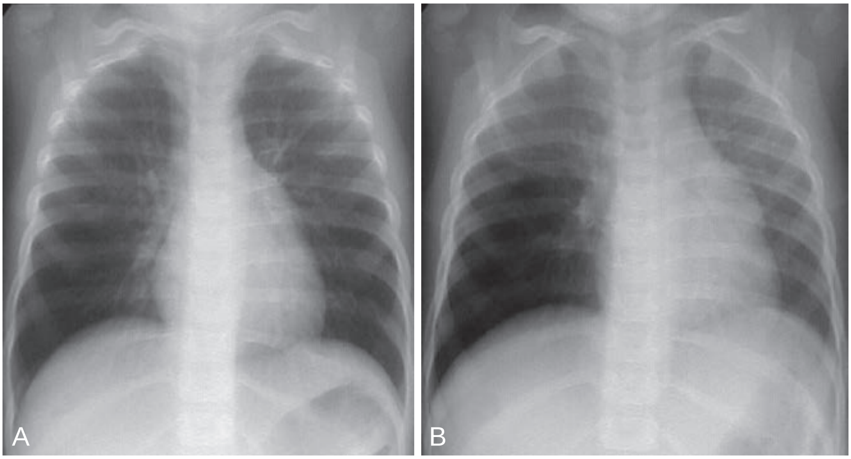

Fig. 16.7 Right-sided foreign-body aspiration. Compared with inspiratory film (A), expiratory film (B) shows continued expansion on the right side due to air trapping caused by the foreign body. (From Pinzoni F, Boniotti C, Molinaro SM. Inhaled foreign bodies in pediatric patients: review of personal experience. *Int J Pediatr Otolaryngol.* 2007;71:1897–1903.)

76. On which side of the chest are foreign-body aspirations and aspiration pneumonias more common?

Right side, particularly in older children and adolescents. This occurs because of anatomic considerations. The right mainstem bronchus, compared with the left, is wider, has a larger airflow, and has a less acute angle with the trachea. This allows for easier passage of both small foreign bodies and aspirated liquids to enter the right side and its secondary airways. This angulation difference is less pronounced in infancy and increases as children age through puberty. Thus the younger the child, the less likely is a right-sided predominance.

77. What are the possible mechanisms for the development of lung abscesses in children?

- **After pneumonia:** particularly Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae, and Klebsiella pneumoniae
- **Hematogenous spread:** especially if an indwelling central catheter or right-sided endocarditis is present
- **Penetrating trauma**
- **Aspiration:** especially in neurologically compromised patients
- **Secondary to infection of an underlying pulmonary anomaly:** such as a bronchogenic cyst

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Campbell PW. Lung abscess. In Hilman BC, ed. *Pediatric Respiratory Disease*. Philadelphia, PA: W.B. Saunders; 1993:257–262.

78. What are the typical clinical findings in patients with bronchiectasis?

Bronchiectasis is the progressive dilation of bronchi, most likely from acute and/or recurrent obstruction and infection. It may result from a variety of infections (e.g., adenoviral, rubeola, pertussis, tuberculosis), and it is often associated with underlying pulmonary susceptibility (e.g., CF, ciliary dyskinesia syndromes, immunodeficiencies). Clinical findings can be variable but usually include bad breath, persistent cough, chronic production of purulent sputum, recurrent fevers, and digital clubbing. Inspiratory crackles are often heard over the affected area. Hemoptysis and wheezing can occur but are uncommon.

Chang AB, Bush A, Grimwood K. Bronchiectasis in children: diagnosis and treatment. *Lancet.* 2018;392(10150):866–879.

79. A novice teenage mountain climber develops headache, marked cough, and orthopnea at the end of a rapid 2-day climb. What is the likely diagnosis?

Acute mountain sickness with high-altitude pulmonary edema. This condition results from insufficient time to adapt to altitude changes above 2500 to 3000 meters, with alveolar and tissue hypoxia occurring as a result of pulmonary hypertension and pulmonary edema. In severe cases, cerebral edema can result. Treatment consists of returning the patient to a lower altitude and administering oxygen. If descent and supplemental oxygen are not

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available, portable hyperbaric chambers and nifedipine or phosphodiesterase-5 inhibitors should be used until descent is possible. If cerebral edema is suspected, dexamethasone is indicated.

Bärtsch P, Swenson ER. Acute high-altitude illnesses. *N Engl J Med.* 2013;368(24):2294–2302.

80. What is the likely diagnosis of a child with diffuse lung disease, microcytic anemia, and sputum that contains hemosiderin-laden macrophages?

Pulmonary hemosiderosis. This condition, the presenting symptoms of which can include chronic respiratory problems or acute hemoptysis, is characterized by alveolar hemorrhage and microcytic hypochromic anemia with a low serum iron level. Hemosiderin ingested by alveolar macrophages can often be detected in sputum or gastric aspirates after staining with Prussian blue. Most commonly, the condition is idiopathic and isolated, but it can be associated with cow milk hypersensitivity (Heiner syndrome), glomerulonephritis with anti–basement membrane antibodies (Goodpasture syndrome), and collagen vascular disease.

81. What are the risk factors for spontaneous pneumothorax?

Pneumothorax is said to be *spontaneous* if it occurs in the absence of evident trauma. It is classified into *primary* (absence of underlying lung disease) or *secondary* (due to underlying lung disease).

Primary spontaneous pneumothorax risk factors include:

- Tall, thin build
- Drug use (tobacco, marijuana, snorting cocaine)
- Activities that cause elevated transpulmonary pressure (Valsalva, scuba diving, unpressurized flight)

Secondary spontaneous pneumothorax risk factors are many, including:

- Airway disease (asthma, CF, foreign-body obstruction)
- Infection (tuberculosis [TB], necrotizing pneumonia, pneumocystis pneumonia)
- Congenital lesions (congenital pulmonary airways malformation [CPAM], congenital lobar emphysema)
- Interstitial lung disease (Langerhans histiocytosis, sarcoidosis)
- Connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome, dermatomyositis)
- Malignancy (primary or metastatic)
- Thoracic endometriosis

82. How should a child with a spontaneous pneumothorax be managed?

Assuming no underlying lung disease, if the pneumothorax is small and the child is asymptomatic, observation alone is appropriate. Administration of 100% oxygen may speed resorption of the free air. If the pneumothorax is larger than 20% to 30% of the hemithorax and/or the patient has evolving respiratory symptoms, evacuation of the pneumothorax is indicated. In stable patients with primary spontaneous pneumothorax, one-time aspiration with a large syringe can be sufficient. Other options include insertion of a pigtail catheter or thoracostomy tube. Signs of tension pneumothorax (e.g., marked dyspnea, tachypnea and tachycardia, unilateral thoracic hyperresonance with reduced breath sounds, tracheal shift) necessitate emergent aspiration and tube placement.

83. What is the recurrence risk with primary spontaneous pneumothorax?

Primary spontaneous pneumothorax has a high risk for recurrence. There are limited data in children, but case series report risks of 20% to 55%, similar to adults. There may be a higher risk associated with the presence of apical blebs. Most experts recommend pleurodesis and resection of blebs (if present) in cases of recurrence, and some advocate this be done with the first episode if the pneumothorax is large.

84. What are the clinical and radiographic features of a tension pneumothorax?

- *Clinical:* Increasing respiratory distress, hypoxemia, hypercarbia, hypotension
- *Radiographic:* Hyperlucency of the hemithorax, shifting of the mediastinum, flattening of the diaphragm, widening of the intercostal spaces (Fig. 16.8)

85. What physical examination features suggest a pleural effusion?

- Dullness to percussion (“stony dullness”)
- Diminished or absent breath sounds on the side of the effusion
- Diminution in tactile fremitus
- Presence of a friction rub on auscultation
- Egophony (“e” to “a” changes)

86. In children with pleural effusions, how are exudates distinguished from transudates?

Exudative pleural effusions meet at least one of the following criteria:

- Pleural fluid protein–to–serum protein ratio of ≥ 0.5
- Pleural fluid lactate dehydrogenase (LDH)–to–serum LDH ratio of > 0.6

- Pleural fluid LDH concentration is >66% of the upper limit of normal for serum

If none of these criteria are met, the patient has a *transudative pleural effusion*. The criteria are extremely sensitive for the identification of exudates, but specificity is much lower. Twenty percent of transudates from CHF may be incorrectly identified as exudates, particularly in the setting of diuretic use, which increases protein and LDH concentration in pleural fluid.

Muzumdar H. Pleural effusion. *Pediatr Rev.* 2012;33(1):44–46.

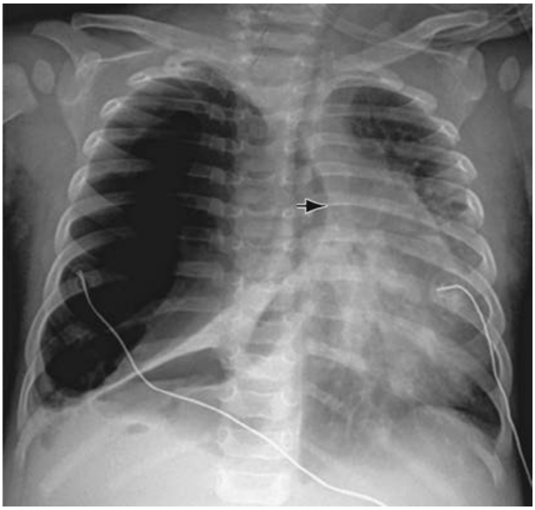

Fig. 16.8 Right tension pneumothorax with shift of the mediastinum to the left *(arrow)*. (From Kliegman RM, St Geme JW, Blum NJ, et al, eds. *Nelson's Textbook of Pediatrics.* 21st ed. Philadelphia, PA: Elsevier; 2010:2319.)

87. What pediatric diseases are associated with exudative versus transudative pleural effusions?

Exudates result from conditions of **increased capillary permeability**, whereas *transudates* occur with **increased capillary hydrostatic pressure**.

Exudative

- Pneumonia
- TB
- Malignancy
- Chylothorax

Transudative

- CHF
- Cirrhosis
- Nephrotic syndrome
- Upper airway obstruction

In children, the most common cause for a pleural effusion is pneumonia ("parapneumonic"), whereas in adults, the most common etiology is CHF.

Beers SL, Abramo TJ. Pleural effusions. *Pediatr Emerg Care.* 2007;23(5):330–334.

88. What are possible treatments for infected parapneumonic effusions?

Although uncomplicated pleural effusions can usually be managed conservatively without the need for surgery, about 5% of patients with pleural effusions progress to empyema (Fig. 16.9). The precise approach to therapy is controversial and often varies by institution, but options include medical management alone or in combination with thoracentesis, chest tube drainage, video-assisted thoracoscopic surgery (VATS) with chest tube drainage, intrapleural fibrinolytic therapy, and thoracotomy. In general, a simple diagnostic and therapeutic thoracentesis is done with insertion of a chest tube in the early exudative phase of an empyema when fluid is accumulating. VATS therapy is more commonly the treatment of choice in early organizing empyemas (a fibrinopurulent phase), whereas thoracotomy, often combined with pleural stripping, is used in later, more advanced empyemas when scar formation can result in lung entrapment.

Griffith D, Boal M, Rogers T. Evolution of practice in the management of parapneumonic effusion and empyema in children. *J Pediatr Surg.* 2018;53(4):644–646.

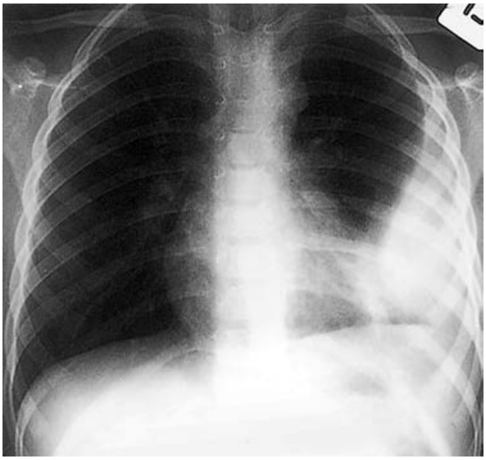

Fig. 16.9 Large left empyema with passive atelectasis of the adjacent lung. (From Chernick V, Boat TF, Wilmott RW, Bush A, eds. *Kendig's Disorders of the Respiratory Tract in Children.* 7th ed. Philadelphia, PA: W.B. Saunders; 2006:374.)

89. What is the value of chest physiotherapy (CPT) in patients with pediatric pulmonary disease?

The main function of *CPT* is to assist with the removal of tracheobronchial secretions to lessen obstruction, reduce airway resistance, enhance gas exchange, and reduce the work of breathing. A variety of techniques are used: chest wall percussion, vibration, and postural drainage. CPT has been advocated in patients with chronic sputum production (e.g., CF), primary pneumonia, and atelectasis; for intubated neonates; and for postextubation and postoperative patients. However, clinical benefits in each category—with the exception of diseases of chronic sputum production—remain highly anecdotal and understudied. Limited evidence does not support a role in bronchiolitis and asthma.

Chaves GS, Freitas DA, Santino TA, et al. Chest physiotherapy for pneumonia in children. *Cochrane Database Syst Rev.* 2019;1:CD010277.

Roque I, Figuis M, Giné-Garriga M, et al. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months. *Cochrane Database Sys Rev.* 2016;2:CD004873.

90. Where is pulmonary surfactant produced?

Pulmonary surfactant is a structured mixture of lipids and proteins that is essential for reducing and equalizing surface tension at the air–liquid interface in alveoli and preventing alveolar collapse. Surfactant is produced by **alveolar type II epithelial cells** and secreted into the airspaces and is removed by alveolar macrophages.

91. What disorders related to surfactant can occur outside of the neonatal period?

- **Genetic disorders of surfactant function** can result from inactivation of surfactant protein genes (*SP-B, SP-C*), lack of gene expression due to loss of necessary transcription factor (*NKX*2.1), or impaired cellular trafficking of surfactant (*ABCA*3). These mutations result in a pattern of interstitial lung disease with both a varying time of presentation (infancy to early childhood) and of severity.
- **Altered surfactant metabolism**: Surfactant is normally cleared by alveolar macrophages. Interference with this process, usually due to alteration of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling, results in accumulation of surfactant in alveolar spaces (pulmonary alveolar proteinosis).

Lopez-Rodriguez E, Gay-Jordi G, Mucci A, et al. Lung surfactant metabolism: early in life, early in disease and target in cell therapy. *Cell Tissue Res.* 2017;367(3):721–735.

92. Who was Ondine, and what was her curse?

Ondine was a mythical water nymph who fell in love with Hans, a mortal. She put a curse on him with the stipulation that should he ever betray her, he would suffocate by not breathing when he fell asleep. Unfortunately, Hans fell for the charms of Bertha, and he eventually succumbed to the curse while dozing. The term *Ondine curse* has been used to describe the syndrome of sleep apnea as a result of reduced respiratory drive, more commonly referred to now as *congenital central hypoventilation syndrome* (CCHS). Patients with CCHS are unable to regulate their ventilatory drive due to loss of vagal input and diminished sensitivity of CO_2 receptors in the medulla, particularly during sleep or in situations of increased metabolic need (e.g., illness).The syndrome is primarily caused by mutations in *PHOX2B,* a regulatory gene active in the nervous system. Patients with CCHS require tracheostomy and mechanical ventilation during sleep, and often while awake as well. An alternative, though not widely available, is phrenic nerve pacing. Other complications of CCHS due to *PHOX2B* mutation include Hirschsprung disease, dysautonomia, ocular abnormalities, and neural-crest-derived tumors (ganglioneuroma, ganglioneuroblastoma).

Zaidi S, Gandhi J, Vatsia S, et al. Congenital central hypoventilation syndrome: an overview of etiopathogenesis, associated pathologies, clinical presentation, and management. *Auton Neurosci.* 2018;210:1–9.

Mellins RB, Balfour HH Jr, Turino GM, Winters RW. Failure of automatic control of ventilation (Ondine's curse). Report of an infant born with this syndrome and review of the literature. *Medicine (Baltimore).* 1970;49(6):487–504.

93. What are the most frequent indications for lung transplantation in children?

Pediatric lung transplantation remains a fairly rare procedure in the United States. In 2019, only 50 lung transplants were performed in recipients <18 years of age. Indications for transplant vary by age, but by far the most common is CF, followed by pulmonary hypertension, pulmonary vascular disease, interstitial lung disease, bronchopulmonary dysplasia, and congenital heart disease. Most children with end-stage lung disease required bilateral transplantation.

Sweet SC. Pediatric lung transplantation. *Respir Care.* 2017;62(6):776–798.

Organ Procurement and Transplantation Network. https://optn.transplant.hrsa.gov/data. Accessed March 9, 2020.

94. What are the outcomes of lung transplantation in children?

The outcomes of lung transplantation are not as favorable as for other solid organ transplants. The 1-year survival rate is 85%, 3-year is 65%, and 5-year is 56%. The main life-limiting complication is bronchiolitis obliterans syndrome (BOS), which occurs in over 70% of recipients by 8 years. BOS is a form of chronic allograft dysfunction, which is characterized by inflammatory and fibrotic changes in the small noncartilaginous airways (bronchioles). Other aspects that limit long-term success include debilitation as a result of chronic disease and risks for infection from immunosuppression.

Benden C. Pediatric lung transplantation. *J Thorac Dis.* 2017;9(8):2675–2683.

Sweet SC. Pediatric lung transplantation. *Respir Care.* 2017;62(6):776–798.

CYSTIC FIBROSIS

95. What is the cause of CF?

Among the Caucasian population, CF is the most common life-shortening autosomal recessive disease. About 1000 new cases are diagnosed annually in the United States. CF is caused by inherited mutations in the **cystic fibrosis transmembrane conductance regulator (*CFTR*) gene**. This gene codes for a surface membrane protein that acts as a chloride channel and regulates other ion channels. Defective function of this protein results in thick, viscous, obstructive secretions in the mucous glands of the airways, pancreatic ducts, and elsewhere, resulting in inflammation and obstruction. This protein is expressed in all exocrine tissues, hence the pleomorphic effects. Over 1800 pathogenic mutations in *CFTR* have been identified.

Ratjen F, Bell SC, Rowe SM. Cystic fibrosis. *Nat Rev Dis Primers.* 2015;1:15010.

O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet.* 2009;373(9678):1891–1904.

96. When did the term *cystic fibrosis* originate?

The first description of the disorder occurred in 1938 when a U.S. pathologist, Dr. Dorothy Anderson, determined the autopsies of some malnourished infants had unique mucus plugging of pancreatic glandular ducts, which she termed "cystic fibrosis of the pancreas." As other areas of the body were noted to have similar mucus clogging of exocrine ducts, the condition also was called *mucoviscidosis* and was known as a generalized exocrinopathy. In 1948, a pediatrician in New York City (Dr. Paul di Sant-Agnese) noticed during a heat wave that many of the infants with heat prostration had clinical features of CF (e.g., steatorrhea, malabsorption, growth failure, pulmonary infection), and he postulated abnormalities in sweat. This hypothesis proved correct when excess sodium and chloride were detected in the sweat of patients with CF. This formed the basis for the diagnostic pilocarpine iontophoresis test (sweat test) of 1959. Thirty years later, in 1989, the CF gene was discovered.

Davis PB. Cystic fibrosis since 1938. *Am J Respir Crit Care Med.* 2006;173(5):475–482.

97. What is the frequency of CF in different populations?

- **Whites:** 1 in 2500 to 3500 live births
- **Hispanic Americans:** 1 in 900[illegible],500 live births

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- **Native Americans:** 1 in 11,000 live births
- **African Americans:** 1 in 15,000 to 17,000 live births
- **Asian Americans:** 1 in 31,000 to 35,000 live births

U.S. National Library of Medicine. Genetics home reference: cystic fibrosis. www.ghr.hlm.nih.gov. Accessed May 20, 2019.
Rohlfs EM, Zhou Z, Heim RA, et al. Cystic fibrosis carrier testing in an ethnically diverse US population. *Clin Chem.* 2011;57(6):841–848.

98. What are the presenting signs and symptoms of CF?

These can be remembered with the acronym **CF PANCREAS**:

- **C**hronic cough and wheezing
- **F**ailure to thrive
- **P**ancreatic insufficiency (signs of malabsorption, including bulky, foul stools)
- **A**lkalosis and hyponatremic dehydration
- **N**eonatal intestinal obstruction (meconium ileus) and **N**asal polyps
- **C**lubbing of the fingers and **C**hest radiographs with changes
- **R**ectal prolapse
- **E**lectrolyte elevation in sweat (salty skin)
- **A**bsence or congenital atresia of the vas deferens
- **S**putum with *Staphylococcus* or *Pseudomonas* (mucoid)

Schidlow DV. Cystic fibrosis. In Schidlow DV, Smith DS, eds. *A Practical Guide to Pediatric Respiratory Diseases.* Philadelphia, PA: Hanley & Belfus; 1994:76.

99. How are most cases of CF diagnosed?

Over 75% of new cases are diagnosed by **newborn screening**. This relies on detection in the blood of *immunoreactive trypsinogen (IRT),* a pancreatic enzyme precursor, which is elevated in most patients with CF at birth. States have different procedures for subsequent testing for mutations in *CFTR*, using either a selected mutation panel or direct sequencing. CF diagnosis outside of the neonatal period relies on clinical evidence as well as evidence of *CTFR* dysfunction. Confirmatory testing at a CF referral center includes measurement of sweat chloride by pilocarpine iontophoresis. Values ≥60 mmol/L are consistent with CF; values between 30 and 59 mmol/L are considered intermediate and prompt further testing; and values ≤29 mmol/L are considered unlikely CF. All suspected CF patients undergo genetic testing.

Both of the following criteria must be met to diagnose CF:

- Clinical symptoms consistent with CF in at least one organ system or positive newborn screen or genetic testing for siblings of patients with CF
- Evidence of *CFTR* dysfunction (any of the following):
  - Elevated sweat chloride ≥60 mmol/L (on two occasions)
  - Presence of two disease-causing mutations in *CFTR*, one from each parental allele
  - Abnormal nasal potential difference

Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr.* 2017;181S:S4–S15.e1.
Sosnay PR, White TB, Farrell PM, et al. Diagnosis of cystic fibrosis in non-screened populations. *J Pediatr.* 2017;181S:S52–S57.e2.

100. How can mutations in CF be categorized?

One rough but important classification is **mild** vs. **severe**. Severe mutations have no residual function and result in clinically more serious disease with pancreatic insufficiency. There are mutations that do preserve some function, and a combination of a severe and a mild mutation usually has a milder phenotype, sometimes with survival of pancreatic function. These genotype–phenotype correlations are quite reliable in CF.

Rational development of therapeutic targets in CF has led to another classification, based on the mechanism through which it affects CFTR:

- *Class I*: nonsense mutations resulting in early termination of translation and no functional protein
- *Class II*: CFTR protein is created, but is structurally unstable and gets targeted for destruction by cellular machinery
- *Class III*: CFTR protein is produced and expressed at the surface, but the chloride channel gating is defective (closed position)
- *Class IV*: CFTR produced, expressed, and able to conduct chloride, but conductance is misregulated
- *Class V*: normal CFTR protein created in insufficient quantity or diminished survival

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Cystic Fibrosis Foundation. 2016 patient registry annual data report. www.cff.org. Accessed May 20, 2019.

101. What is the most common mutation in patients with CF?

F508del. This involves a deletion of the triplet codon that codes for phenylalanine at amino acid position 508, resulting in an unstable protein that gets targeted for destruction. In CF patients in the United States, 46% of patients are homozygous for F508del and 41% are compound heterozygotes for F508del and another mutation.

Cystic Fibrosis Foundation. 2016 patient registry annual data report. www.cff.org. Accessed May 20, 2019.

102. What is the predicted survival of a patient with CF?

From the first attestations of what was probably CF, survival was dismal. A European folk saying from the Middle Ages warned, "woe is the child who tastes salty from a kiss on the brow, for he is cursed, and soon must die." Even in the first part of the twentieth century, survival was rarely over 1 year. Since then, with enormous advances in antimicrobial treatment, nutritional support, and organization of care, by 2001, predicted median survival was 34 years. Progress is continuing; for those born in 2018, median expected survival was 47.4 years. Further gains are anticipated with increased use of new CFTR modulator drugs.

Cystic Fibrosis Foundation. 2018 patient registry annual data report. www.cff.org. Accessed March 11, 2020.
Quinton PM. Physiological basis of cystic fibrosis: a historical perspective. *Physiol Rev.* 1999;79(1 Suppl):S3–S22.

103. Is CF still primarily a pediatric disease?

No. Though typically CF is thought of as a pediatric disease, the number of adults living with it now exceeds that of children with CF. The differential continues to grow, reflecting improved survival with each cohort and the need to coordinate efficient transition of care.

Coyne I, Sheehan AM, Heery E, While AE. Improving transition to adult healthcare for young people with cystic fibrosis: a systematic review. *J Child Health Care.* 2017;21(3):312–330.

104. Which features of CF have prognostic significance?

- **Gender:** Males have better survival rates than females, although the gap is narrowing.
- **Colonization with virulent bacteria:** *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* (MRSA), and *Burkholderia cepacia* are more serious pathogens, which are often resistant to multiple drugs and are difficult to clear after the patient becomes persistently infected. *Stenotrophomonas maltophilia* is an emerging problem; patients who are chronically colonized with these organisms have significantly poorer survival rates than other patients with CF.
- **Diabetes mellitus** is a negative prognostic factor that is associated with increased rates of decline in pulmonary function.
- **Malnutrition** is also associated with increased rates of decline in pulmonary function.
- **Cor pulmonale** is one of the late complications of CF because progressive obstructive airway disease leads to the development of pulmonary hypertension and respiratory failure. The patient's prognosis is poor after the development of cor pulmonale.
- **Pneumothorax** is associated with moderate to advanced lung disease in patients with CF. Therefore air leak has traditionally been regarded as a poor prognostic sign. The prognosis has been improving now that pneumothoraces are being managed aggressively.
- **Worsening pulmonary function tests:** Patients with FEV_1 $<$30% of predicted have an increased 2-year mortality rate.

Breuer O, Caudri D, Stick S, Turkovic L. Predicting disease progression in cystic fibrosis. *Expert Rev Respir Med.* 2018;12(11):905–917.
Montgomery GS, Howenstine M. Cystic fibrosis. *Pediatr Rev.* 2009;30(8):302–309.

105. When and why should children with CF be screened for possible CF-related diabetes mellitus?

Children with CF should be screened for possible CF-related diabetes mellitus **after 10 years of age**. Thick viscous secretions in CF patients cause obstructive damage to the exocrine pancreas, which ultimately can lead to islet cell destruction and diminished insulin production. Annual glucose tolerance testing is recommended after 10 years of age. The hemoglobin A_1C test is not sufficient as a screen because it has poor sensitivity.

Moheet A, Moran A. CF-related diabetes: containing the metabolic miscreant of cystic fibrosis. *Pediatr Pulmon.* 2017;52(S48):S37–S43.
Paranjape SM, Mogayzel PJ Jr. Cystic fibrosis. *Pediatr Rev.* 2014;35(5):194–204.

106. What are the mainstays of pulmonary therapy for children with CF?

- **Airway clearance techniques** (e.g., CPT, mechanical vests, flutter valve)
- **Mucolytic agents** (e.g., recombinant human DNAse, hypertonic saline aerosols)
- **Anti-inflammatory agents** (e.g., ibuprofen, oral azithromycin)
- **Bronchodilators** (e.g., inhaled beta-2 agonists)

- **Antibiotics** (oral, inhaled, and intravenous)
- **CFTR modulators** for appropriate genotypes (ivacaftor, elexacaftor-tezacaftor-ivacaftor)

De Boeck K, Amaral MD. Progress for therapies for cystic fibrosis. *Lancet Respir Med.* 2016;4(8):662–674.
O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet.* 2009;373(9678):1891–1904.

107. What are CFTR modulators?

CFTR modulators are a new generation of drugs that target specific molecular and cellular pathways to restore CFTR function. The effects depend on the specific mutation involved, and thus are approved only for specific mutations or classes of mutations within CF. Currently approved are a potentiator (ivacaftor), which enhances CFTR chloride channel opening, and three correctors (elexacaftor, lumacaftor and tezacaftor), which improve trafficking of mutant CFTR protein. A fixed-dose combination of elexacaftor, tezacaftor, and ivacaftor has been approved for the treatment of CF patients who have at least one F508del mutation. Together, current CFTR modulators are applicable to 90% of all patients with CF. More candidates are in development to improve CFTR function for all classes of mutations. However, there is ongoing controversy due to the astronomical cost of these therapies ($250,000 to $300,000 per year).

Grasemann H. CFTR modulator therapy for cystic fibrosis. *N Engl J Med.* 2017;377(21):2085–2088.

KEY POINTS: CYSTIC FIBROSIS

1. Cystic fibrosis is the most common lethal inherited disease in Caucasians, with an autosomal recessive inheritance pattern, due to mutations in the *CFTR* gene.
2. There are over 1800 known mutations in CFTR, with F508del as the most common.
3. Pulmonary disease is due to a self-reinforcing cycle of inflammation, obstruction, and infection in the airways.
4. CFTR is expressed in exocrine secretory tissues; other involved systems include gastrointestinal (intestinal obstruction, malabsorption, rectal prolapse, cholestasis), endocrine (diabetes), and reproductive (male infertility)
5. Survival and quality of life with CF have been steadily improving with supportive measures, and progress is expected to accelerate with the development of therapies that partially restore CFTR function.

PNEUMONIA

108. What agents cause pneumonia in children?

See Table 16.3. Epidemiology involving the novel coronavirus (COVID-19) for children is evolving.

Table 16.3 Agents That Cause Pneumonia

AGE	VIRAL	BACTERIAL	ATYPICAL
Birth to 3 wk	Cytomegalovirus Herpes simplex virus	Group B streptococcus Gram-negative enteric bacilli (e.g., *Escherichia coli*) *Listeria monocytogenes*	*Ureaplasma urealyticum*
3 wk to 3 mo	Respiratory syncytial virus Parainfluenza viruses Human metapneumovirus Influenza A and B Adenovirus Bocavirus Rhinovirus	*Streptococcus pneumoniae* *Bordetella pertussis* *Staphylococcus aureus*	*Chlamydia trachomatis*
3 mo to 5 yr	Respiratory syncytial virus Parainfluenza viruses Influenza A and B Human metapneumovirus Adenovirus Bocavirus Rhinovirus	*Streptococcus pneumoniae* *Haemophilus influenzae* (nontypeable) *Staphylococcus aureus*	*Mycoplasma pneumoniae* *Chlamydophila pneumoniae*
5 yr to adolescence	Influenza A and B	*Streptococcus pneumoniae* *Staphylococcus aureus*	*Mycoplasma pneumoniae* *Chlamydophila pneumoniae*

109. What are important trends in the etiology of pneumonia in the United States?

- **Bacterial:** The introduction of the pneumococcal conjugate vaccines has substantially reduced hospitalizations for pneumonia.
- **Viral:** Viral pneumonia is more common in younger age groups and most frequently is due to RSV. Human metapneumovirus, described initially in 2001, can mimic the clinical picture of RSV. Data on the involvement of the novel coronavirus (COVID-19) as a cause of pneumonia in children are evolving.
- **Atypical pneumonia:** Caused by *Mycoplasma pneumoniae* and *Chlamydophila* (formerly *Chlamydia*) *pneumoniae,* these infections were previously thought to be uncommon in preschool-age children. In this age group, the incidence is thought to be increasing. Both organisms become more prevalent in school-age children and are the most common etiology for pneumonia in older children.

Wiese AD, Griffin MR, Grijalva CG. Impact of pneumococcal vaccines on hospitalizations for pneumonia in the United States. *Expert Rev Vaccines.* 2019;18(4):327–341.

110. Are throat or nasopharyngeal cultures helpful for the diagnosis of pneumonia?

As a rule, the correlation between throat and nasopharyngeal bacterial cultures and lower respiratory tract pathogens is poor and of **limited value**. Healthy children may be colonized with a wide variety of potentially pathologic bacteria (e.g., *S. aureus*, nontypeable *H. influenzae*), which can be considered part of the normal flora; *Bordetella* pertussis is an exception. Polymerase chain reaction (PCR) studies to identify respiratory viruses, *C. pneumoniae,* or *M. pneumoniae* are more useful because these organisms are much less commonly carried asymptomatically.

111. How often are blood cultures positive in children with suspected bacterial pneumonia?

In the era of pneumococcal vaccination, blood cultures are positive **<3%** of the time in children hospitalized in non–intensive care unit (ICU) settings with presumed bacterial community-acquired pneumonia. The incidence of bacteremia is unclear because the true denominator in the equation (the number of true bacterial pneumonias) is difficult to ascertain due to imprecision with making a definitive diagnosis. The low rate of positive blood cultures does suggest that most bacterial pneumonias are not acquired by hematogenous spread.

Neuman MI, Hall M, Lipsett SC, et al. Utility of blood culture among children hospitalized with community-acquired pneumonia. *Pediatrics.* 2017;140(3):e20171013.

112. Can a chest radiograph reliably distinguish between viral and bacterial pneumonia?

No. Viral infections more commonly have multifocal interstitial, perihilar, or peribronchial infiltrates; hyperinflation; segmental atelectasis; and hilar adenopathy. Effusions are uncommon. However, there can be considerable overlap in features with bacterial (and *Chlamydophila* and *Mycoplasma*) pneumonia. Bacterial pneumonia more commonly results in lobar and alveolar infiltrates, but the sensitivity and specificity of this finding are not very high.

Kronman MP, Shah SS. Pediatric community-acquired pneumonia. *Contemp Pediatr.* 2009;26:44–50.

113. What are indications for hospital admission in children with pneumonia?

- All who are toxic, dyspneic, or hypoxic
- Suspected staphylococcal pneumonia (e.g., pneumatocele on chest radiograph) (Fig. 16.10)
- Moderate or large pleural effusion
- Suspected aspiration pneumonia (because of the higher likelihood of progression)
- Children who cannot tolerate oral medications or who are at significant risk for dehydration
- Suspected bacterial pneumonia in very young infants, especially with multilobar involvement
- Poor response to outpatient therapy after 48 hours
- Those whose family situation and chances for reliable follow-up are suboptimal

114. What clinical clues suggest atypical pneumonia?

Atypical pneumonia refers to one caused by certain bacteria, including *M. pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila*. Characteristically, these infections start gradually, have minimal or a nonproductive cough, and have frequent nonrespiratory symptoms and signs (e.g., headache, rash, and pharyngitis). Chest radiographs tend to show patchy, peribronchial infiltrates with only occasionally lobar consolidation.

115. What are the clinical characteristics of chlamydial pneumonia in infants?

- Illness occurs between 2 and 19 weeks after birth. Most infants are symptomatic by 8 weeks of age.
- Onset is gradual, with upper respiratory prodromal symptoms lasting longer than 1 week.
- Nearly 100% of patients are afebrile.
- Less than half have inclusion conjunctivitis.
- Respiratory signs and symptoms include the following: staccato cough, tachypnea, diffuse crackles, and occasional wheezing.
- Chest radiograph reveals bilateral hyperexpansion and symmetric interstitial infiltrates.
- Seventy percent have an elevated absolute eosinophil count ($>400/\text{mm}^3$).
- More than 90% have increase titative immunoglobulins.

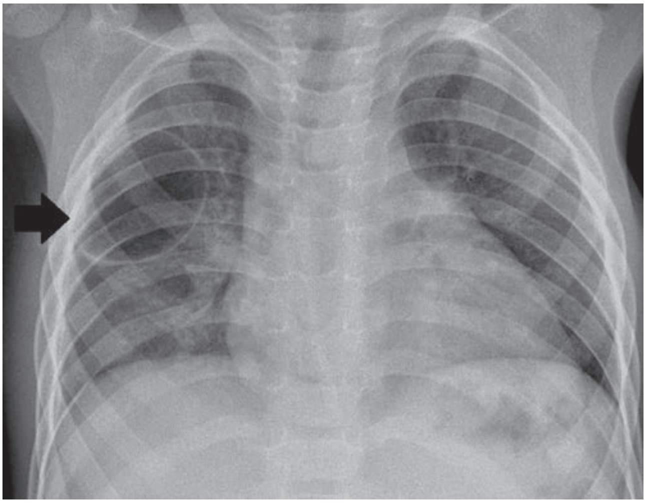

Fig. 16.10 Pneumatocele after severe staphylococcal pneumonia (a thin-walled cyst in the right upper zone *[arrow]*). (From Adam A, Dixon AK, Gillard JH, et al. *Grainger & Allison's Diagnostic Radiology.* 6th ed. Philadelphia, PA: Elsevier; 2015:1789.)

116. How helpful are cold agglutinins in the diagnosis of *M. pneumoniae* infections?

Cold agglutinins are immunoglobulin M (IgM) autoantibodies that are directed against the I antigen of erythrocytes, which agglutinate red blood cells at 39.2°F (4°C). Up to 75% of patients with *Mycoplasma* infections will develop them, usually toward the end of the first week of illness, with a peak at 4 weeks. A titer of 1:64 supports the diagnosis. Other infectious agents, including adenovirus, cytomegalovirus, Epstein-Barr virus, influenza, rubella, *Chlamydia,* and *Listeria,* can also give a positive result. A single cold agglutinin titer of 1:64 is therefore suggestive, but not conclusive, evidence of infection with *M. pneumoniae*. More definitive testing requires immunoglobulin G (IgG) and IgM serology (especially acute and convalescent titers), quantitative polymerase chain reaction (FQ-PCR), and culture. The increased availability of multiplex PCR capable of detecting *M. pneumoniae* has decreased reliance on the much less specific cold agglutinin test.

Qu J, Wu J, Dong J, et al. Accuracy of IgM antibody testing, FQ-PCR and culture in laboratory diagnosis of acute infection by *Mycoplasma pneumoniae* in adults and adolescents with community-acquired pneumonia. *BMC Infect Dis.* 2013;13:172.

117. When do the radiologic findings of pneumonia resolve?

Although there is a wide range, as a rule, most infiltrates that result from *S. pneumoniae* resolve in 6 to 8 weeks, and those that are caused by RSV resolve in 2 to 3 weeks. However, with some viral infections (e.g., adenovirus), it may take up to 1 year for radiographs to normalize. If significant radiologic abnormalities persist for >6 weeks, there should be a high index of suspicion for a possible underlying problem (e.g., unusual infection, anatomic abnormality, immunologic deficiency).

Regelmann WE. Diagnosing the cause of recurrent and persistent pneumonia in children. *Pediatr Ann.* 1993;22(9):561-568.

118. Do children with pneumonia need follow-up radiographs to verify resolution?

Generally, no. Exceptions would include children with pleural effusions, those with persistent or recurrent signs and symptoms, and those with significant comorbid conditions (e.g., immunodeficiency).

Mahmood D, Vartzelis G, McQueen P, Perkin MR. Radiological follow-up of pediatric pneumonia: principle and practice. *Clin Pediatr (Phila).* 2007;46(2):160–162.

119. What are the causes of recurrent pneumonia?

- **Aspiration susceptibility:** oropharyngeal incoordination, vocal cord paralysis, gastroesophageal reflux, tracheoesophageal fistula
- **Immunodeficiency:** congenital, acquired
- **Abnormal secretions or reduced clearance of secretions:** CF, ciliary dyskinesia, neuromuscular disease

- **Pulmonary anomalies:** sequestration, cystic adenomatoid malformation
- **Airway compression or obstruction:** foreign body, vascular ring, enlarged lymph node, malignancy

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Brand PL, Hoving MF, de Groot EP. Evaluating the child with recurrent lower respiratory tract infections. *Paediatr Respir Rev.* 2012;13(3):135–138.
Kaplan KA, Beierle EA, Faro A, et al. Recurrent pneumonia in children: a case report and approach to diagnosis. *Clin Pediatr (Phila).* 2006;45(1):15–22.

120. How should children with aspiration pneumonitis be managed?

Acute aspiration can often be treated supportively (supplemental oxygen, airway clearance) without antibiotics because the initial process is a *chemical pneumonitis*. If secondary signs of infection occur concerning for an aspiration *pneumonia,* antibiotics should be started after appropriate cultures (e.g., blood, bronchoalveolar lavage) are obtained. Either penicillin or clindamycin is a reasonable choice to cover the oropharyngeal anaerobes that predominate. If the aspiration is nosocomial, antibiotic coverage should be extended to include gram-negative organisms.

Neill S, Dean N. Aspiration pneumonia and pneumonitis: a spectrum of infectious/noninfectious diseases affecting the lung. *Curr Opin Infect Dis.* 2019;32(2):152–157.

KEY POINTS: PNEUMONIA

1. Effusion or pneumatocele suggests a bacterial cause.
2. Radiographic findings in patients with *Mycoplasma* infections are highly variable.
3. In one-half of patients with *Chlamydial* pneumonia, conjunctivitis precedes pneumonia.
4. Yield of blood cultures for community-acquired pneumonia is very low.
5. Recurrent episodes of pneumonia should prompt evaluation for other underlying conditions.

PULMONARY PRINCIPLES

121. In addition to underlying immunologic immaturity, why are infants more susceptible to an increased severity of respiratory disease?

- Very compliant chest wall (allows passage through birth canal but limits inspiratory effort as it distorts with increased respiratory loading)
- Respiratory muscles are more easily fatigued as a result of decreased muscle mass and fewer type I muscle fibers (slow-twitch, high-oxidative fibers)
- Chest wall elastic recoil is low in infancy (airway closure occurs at a higher relative lung volume)
- High airway compliance facilitates airway collapse and air trapping
- Collateral ventilation is poorly developed, thus increasing the likelihood of atelectasis during illness
- Higher airway mucous gland concentration in infants than in adults

122. At what age do alveoli stop increasing in number?

Although extra-acinar airway development is complete by 16 weeks of gestation, alveolar multiplication continues after birth. Early studies suggested that postnatal alveolar multiplication ended around 8 years of age. More recent studies indicate that, on the one hand, new alveoli may be formed into adolescence and adulthood, but exponential growth in alveolar number is largely complete by 2 years of age under normal conditions. After the end of alveolar multiplication, the alveoli continue to increase in size until thoracic growth is completed.

Herring MJ, Putney LF, Wyatt G, et al. Growth of alveoli during postnatal development in humans based on stereological estimation. *Am J Physiol Lung Cell Mol Physiol.* 2014;307(4):L388–344.

123. What is the normal respiratory rate in otherwise healthy children?

Rates in children who are awake can be widely variable, depending on their psychological state and activity. Rates while sleeping are much more reliable and are a good indicator of pulmonary health. As a general rule in an afebrile, otherwise healthy and calm, resting infant or child, the expected maximal respiratory rate declines with increasing age. In the absence of other signs and symptoms, term newborns breathe up to a mean of 50 breaths per minute, decreasing to 40 breaths per minute by 6 months and to 30 breaths per minute at 1 year. Beyond 1 year of age, the rate declines gradually, reaching the typical adult rate of 12 to 20 breaths per minute by the middle teenage years. Counting respiratory rates over 1 minute gives a more accurate measurement than extrapolating rates over shorter time intervals.

124. What is normal oxygen saturation in healthy infants who are <6 months?

In longitudinal studies using pulse oximetry, baseline saturation was higher than 95% (normal was 98%, with the lower tenth percentile at 95%). However, brief desaturations are common in both term and preterm infants; only some are associated with brief episodes of apnea while sleeping.

Hunt CE, Corwin MJ, Weese-Mayer DE, et al. Longitudinal assessment of hemoglobin oxygen saturation in preterm and term infants in the first six months of life. *J Pediatr.* 2011;159(3):377–383.e1.

Hunt CE, Corwin MJ, Lister G, et al. Longitudinal assessment of hemoglobin saturation in healthy infants during the first six months of life. *J Pediatr.* 1999;135(5):580–586.

125. What is the difference between Kussmaul, Cheyne-Stokes, and Biot types of breathing patterns?

- *Kussmaul*: Deep, slow, regular respirations with prolonged exhalation; seen in diabetic ketoacidosis and salicylate ingestion
- *Cheyne-Stokes*: Crescendo-decrescendo respirations alternating with periods of apnea (no breathing); causes include heart failure, uremia, central nervous system trauma, increased intracranial pressure, and coma
- *Biot* (also known as ataxic breathing): Characterized by unpredictable irregularity; breaths may be shallow or deep and stop for short periods; causes include respiratory depression, meningitis, encephalitis, and central nervous system lesions involving the respiratory centers

126. How does the pulse oximeter work?

The key principle behind pulse oximetry is that oxygenated hemoglobin allows for more transmission of certain wavelengths of red light than does reduced hemoglobin. By contrast, transmission of infrared light is unaffected by the amount of oxyhemoglobin present. A light source of red and infrared wavelengths is applied to an area of the body thin enough that the light can traverse a pulsating capillary bed and be detected by a light detector on the other side. Each pulsation increases the distance the light has to travel, which increases the amount of light absorption. A microprocessor derives the arterial oxygen saturation by comparing absorbencies at baseline and during the peak of a transmitted pulse.

Sinha I, Magell SJ, Halfhide C. Pulse oximetry in children. *Arch Dis Child Educ Pract Ed.* 2014;99(3):117–118.

127. What are the disadvantages or limitations of pulse oximetry?

- Patient movement disturbs measurements.
- Poor perfusion states affect accuracy.
- Fluorescent or high-intensity light can interfere with results.
- It is unreliable if abnormal hemoglobin is present (e.g., methemoglobin).
- Accuracy diminishes with arterial saturations below 70% to 80%.

128. How is oxygen carried in the blood?

Oxygen is carried in the blood in two forms: (1) **bound to hemoglobin** and (2) **as free O_2 molecules dissolved in the liquid phase**. The amount of hemoglobin-bound O_2 is 1.34 mL/gram Hgb × $\text{Sa}o_2$ and that of free O_2 dissolved in blood is 0.003 mL/mm Hg[O_2] per dL of blood. Free O_2 is a tiny fraction of the total (1% to 2%) and can generally be ignored.

129. What is the effect of doubling the partial pressure of oxygen on total oxygen-carrying capacity under normal physiologic conditions?

Not much. Assuming a normal value of hemoglobin of 15 g/dL and a starting $\text{Pa}o_2$ at 100 mm Hg, doubling the $\text{Pa}o_2$ to 200 mm Hg will double the amount of dissolved oxygen from 0.3 mL/dL to 0.6 mL/dL. The amount of hemoglobin-bound O_2 changes minimally (due to increased saturation from 98% to 100%) from 19.7 mL/dL to 20.1 mL/dL. The total O_2 content goes from 20 mL/dL to 20.7 mL/dL, or only a 3.5% difference.

130. What is the oxyhemoglobin dissociation curve?

The *oxyhemoglobin dissociation curve,* also called the *oxygen-hemoglobin dissociation curve,* plots how the number of O_2 molecules bound to hemoglobin vary with the partial pressure of O_2 in the blood and tissues (Fig. 16.11). As O_2 partial pressure increases, hemoglobin saturation increases, but not in a linear fashion. There is a sigmoid shape due to the changing affinity of hemoglobin for oxygen molecules at the four carrying sites of hemoglobin. Consequently, there is a range where $\text{Sp}o_2$ is very responsive to $\text{Pa}o_2$ and a flat portion (particularly after a $\text{Pa}o_2$ of 70 mm Hg) where there is not much change in saturation. At a $\text{P}o_2$ of 60 mm Hg, hemoglobin is ≈91% saturated. Increasing $\text{Pa}o_2$ from 60 to 70 mm Hg increases $\text{Sp}o_2$ from 91% to 94%, whereas increasing $\text{Pa}o_2$ from 90 to 100 mm Hg only increases $\text{Sp}o_2$ from 97% to 98%.

131. What factors result in shifting of the oxyhemoglobin dissociation curve?

Several physiologic factors can result in a shift (see Fig. 16.11):

- *Left shifts* occur in settings of **decreased temperature**, **decreased Pco_2**, **alkalosis (↑ pH)**, **increased fetal hemoglobin** (higher affinity for O_2 than adult hemoglobin), and **decreased levels of 2,3-BPG** (2,3-biphosphoglycerate; formerly called *2,3-diphosphoglycerate*). 2,3-BPG is a metabolic intermediary formed during anaerobic glycolysis in mature red blood cells that lack mitochondria. Increased amounts of methemoglobin (MetHgb) and sulfhemoglobin (SfHgb) also result in left shifting, but typically pathologic rather than compensatory. Left shifts result in increased affinity, which aids in increased uptake and binding of O_2 to hemoglobin in the lung, which can be seen in high-altitude scenarios associated with hyperventilation.
- *Right shifts* occur in the opposite: **increased temperature**, **increased Pco_2**, **acidosis (↓ pH)**, and **increased 2,3-BPG**. Right shifts foster the release of O_2 into tissues and cells, as might be needed during periods of increased metabolism, such as exercise.

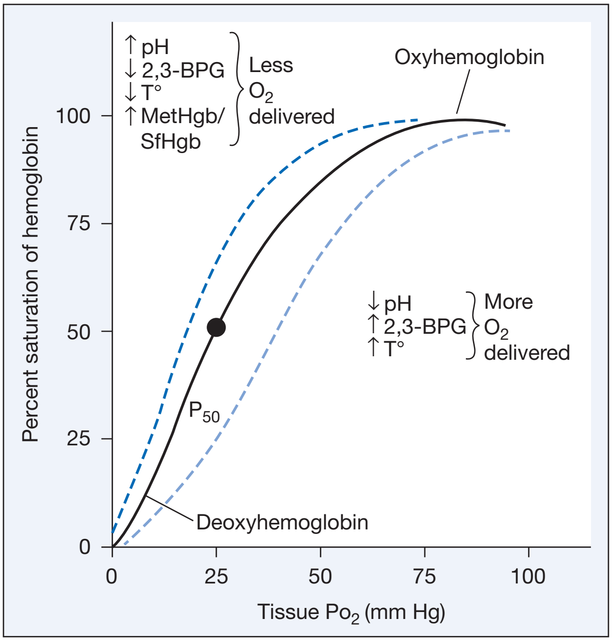

Fig. 16.11 Oxyhemoglobin dissociation curve. Solid line represents the percent of hemoglobin (Hgb) at a given Pao_2.The dashed line to the right (right shift) represents factors that favor O_2 delivery to the tissues. The dashed line to the left (left shift) favors more O_2 binding. P_{50} represents the Po_2 at which hemoglobin is 50% saturated with oxygen, which, outside of the newborn period, is approximately 27 mm Hg. (From Walls RM, Hockberger RS, Gausche-Hill M, eds. *Rosen's Emergency Medicine: Concepts and Clinical Practice.* 9th ed. Philadelphia, PA: Elsevier; 2018:109.)

132. At what concentration is inspired oxygen toxic?

In addition to atelectasis, high oxygen concentration can cause alveolar injury with edema, inflammation, fibrin deposition, and hyalinization. The precise level of hyperoxia that results in injury is unclear and varies by age and underlying lung pathology, but a reasonable rule is to assume that a concentration of more than 80% for >36 hours is likely to result in significant ongoing damage; 60% to 80% is likely to be associated with more slowly progressive injury. An inspired oxygen concentration of 50%, even when administered for extended periods, is unlikely to cause pulmonary toxicity.

Walsh BK, Smallwood CD. Pediatric oxygen therapy: a review and update, *Respir Care.* 2017;62(6):645–661.
Bryan CL, Jenkinson SG. Oxygen toxicity. *Clin Chest Med.* 1988;9(1):141–152.

133. Why is a child who is receiving 100% oxygen more likely to develop atelectasis than one who is breathing room air?

Oxygen is efficiently absorbed from alveoli, whereas nitrogen is not. In room air (which has 78% nitrogen), alveolar collapse is minimized by the continued presence and pressure of nitrogen gas (the "nitrogen stent"). With 100% oxygen breathing, however, the high solubility of oxygen in blood can lead to *absorption atelectasis* in areas of poor ventilation and intrapulmonary shunting.

134. At what PaO_2 does cyanosis develop?

Cyanosis develops when the concentration of desaturated (i.e., reduced) hemoglobin is at least 3 gm/dL centrally or 4 to 6 g/dL peripherally. However, multiple factors affect the likelihood that a given PaO_2 will result in clinically apparent cyanosis: anemia (less likely), polycythemia (more likely), reduced systemic perfusion or cardiac output (more likely), and hypothermia (more likely). Cyanosis is generally a sign of significant hypoxia. In a patient with adequate perfusion and a normal hemoglobin, central cyanosis is commonly noted when the PaO_2 is about 50 mm Hg.

135. What are the causes of a reduced PaO_2 associated with an increased A-aDO_2 (alveolar-arterial oxygen tension difference or A-a gradient)?

- **Right-to-left shunting:** Intracardiac; pulmonary arteriovenous malformations, ventilation-perfusion mismatching that result from perfusion of airless alveoli (e.g., pneumonia, atelectasis). A small degree of shunting is normal (physiologic shunt) due to partial return of bronchial artery flow via pulmonary veins.
- **Maldistribution of ventilation:** Asthma, bronchiolitis, atelectasis, other lung pathology.
- **Impaired diffusion:** An uncommon mechanism because many of the conditions previously thought to have a “diffusion block” (e.g., respiratory distress syndrome) also have a major component ventilation-perfusion mismatch; may be seen when interstitial edema affects the septal walls (e.g., in early pulmonary edema and interstitial pneumonia).
- **Decreased central venous oxygen content:** As a result of a sluggish circulation (e.g., shock) or increased tissue oxygen demands (e.g., sepsis).

136. What are the causes of a reduced PaO_2 associated with a normal A-aDO_2?

- **Low inspired O_2:** such as high altitude or under experimental situations
- **Hypoventilation:** narcotic overdose, anesthesia, respiratory muscle weakness

137. Why do we sigh?

A sigh is just a sigh in *Casablanca*, but it is also a maneuver to recruit alveoli and prevent atelectasis. It is a breath that is at a higher-than-normal tidal volume. Spontaneously breathing humans have a dedicated structure in the brainstem that periodically generates sigh breaths. Patients on mechanical ventilators can be programmed to receive “sigh breaths” at a set frequency, which may improve gas exchange and lung mechanics.

Moraes L, Santos CL, Santos RS, et al. Effects of sigh during pressure control and pressure support ventilation in pulmonary and extrapulmonary mild acute lung injury. *Crit Care.* 2014;18(4):474.

138. Is there a respiratory basis for yawning?

Although a respiratory function for yawning is frequently suggested, scientific support for this belief is minimal. Increasing the concentration of CO_2 in inspired air increases the respiratory rate but does not change the rate of yawning. Relief of hypoxia and opening areas of microatelectasis are other theories that are not supported by scientific studies. Some authors hypothesize that yawning may be an arousal reflex, as yawning may enhance intracranial circulation. Contagious yawning is a well-documented phenomenon in humans (particularly on morning rounds) and in some nonhuman primates (e.g., birds, dogs).

Krestel H, Bassetti CL, Walusinski O. Yawning—its anatomy, chemistry, role, and pathological considerations. *Prog Neurobiol.* 2018;161:61–78.

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CHAPTER 17

RHEUMATOLOGY

Carlos D. Rosé, MD, CIP, Elizabeth Candell Chalom, MD
and Andrew H. Eichenfield, MD

CLINICAL ISSUES

1. What is an antinuclear antibody (ANA)?

ANA is made up of circulating γ-globulins directed against several known and unknown nuclear proteins. Unfortunately, the classic immunofluorescence technique is being replaced by a still nonvalidated enzyme-linked immunosorbent assay (ELISA) technique to save costs. When it is measured by an immunofluorescent technique, it is also called *fluorescent antinuclear antibody* (FANA). It is expressed as a titer, usually with a cutoff of 1:40. It is positive in 97% of patients with systemic lupus erythematosus (SLE), usually at a titer at or above 1:320, and in 60% to 80% of patients with juvenile idiopathic arthritis (JIA), usually at a lower titer. It is also positive in about 11% of normal children, and because of that should not be used as a screening test when the child does not present objective physical findings of arthritis.

Satoh M, Chan EK, Ho L, et al. Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. *Arthritis Rheum.* 2012;64(7):2319–2327.

2. What is an ANA profile?

Out of the many nuclear antigens that can make the FANA test positive, there are some with clinical value in pediatrics. They are grouped under the so-called *ANA profile.* These are individual antibodies measured by ELISA (commercial laboratories) or Western blot (specialized laboratories).

3. Should I order a profile instead of an ANA because it has more specificity?

No. This test has value only in the right clinical context (see later) and when there is a documented positive ANA by immunofluorescence. One exception is anti-Ro antibodies, which may be associated with ANA negativity.

4. What is the significance of the various antibodies included in the ANA profile?

- **Anti–double-stranded DNA:** Associated with SLE. This test has to be ordered separately; it is not usually part of the profile.
- **Antihistone:** Associated with drug-induced lupus.
- **Anti-Ro** (also called *anti-SS A*): Associated with Sjögren syndrome and neonatal lupus.
- **Anti-La** (also called *anti-SS B*): Associated with Sjögren syndrome and neonatal lupus.
- **Anti-RNP:** Associated with SLE and with mixed connective tissue disease (MCTD).
- **Anti-topoisomerase** (also called *anti-scleroderma*): Associated with diffuse systemic scleroderma.
- **Anti-centromere:** Associated with limited systemic scleroderma.
- **Anti-Jo-1:** Associated with a subset of patients with polymyositis.

5. A 6-year-old girl with a 2-month history of joint pain (onset after a viral illness) has a normal physical examination, complete blood cell count, and erythrocyte sedimentation rate (ESR) but a positive ANA titer of 1:160. What are some of the possible explanations for this positive ANA?

- Laboratory variation
- Nonspecific response to viral illness
- Preclinical state of SLE (least likely)
- Normal population frequency (about 8% at that titer)
- Other autoimmune or paraneoplastic conditions

Tan EM, Feltkamp TE, Smolen JS, et al. Range of antinuclear antibodies in “healthy” individuals. *Arthritis Rheum.* 1997;40(9):1601–1611.

6. Is Raynaud phenomenon a disease?

In 1874, Maurice Raynaud, while still a medical student, described a triad of episodic pallor, cyanosis, and erythema after exposure to cold stress; the term *Raynaud phenomenon* describes this clinical triad. When this phenomenon is associated with a disease such as scleroderma or lupus, it is called *Raynaud syndrome;* when the phenomenon is seen as an isolated condition without any other rheumatic disorder, it is called *Raynaud disease,* although some patients on long-term follow-up may develop an associated disease (e.g., systemic scleroderma). Rheumatologists are commonly consulted for adolescents with blue, dusky hands and feet. If there is no pallor, it is probably acrocyanosis (*Crocq disease*), a benign variant of no clinical relevance. It may occur in association with weight loss in athletes or children treated with amphetamine derivatives for attention-deficit/hyperactivity disorder.

Wigley FM, Flavahan NA. Raynaud's phenomenon. *N Engl J Med.* 2016;375(6):556-565.
Nigrovic PA, Fuhlbrigge RC, Sundel RP. Raynaud's phenomenon in children: a retrospective review of 123 patients. *Pediatrics.* 2003;111(4 Pt 1):715–721.

7. When is a child considered to have hypermobile joints?

The presence of three of the following features suggests true hypermobility:

- Apposition of the thumb to the flexor aspect of the forearm (Fig. 17.1)
- Hyperextension of the fingers so that they lie parallel to the dorsum of the forearm
- Hyperextension at the elbow of >10 degrees
- Knee hyperextension of >10 degrees
- Ability to touch the floor with the heel and also with the palms of the hands from a standing position without flexing the knee

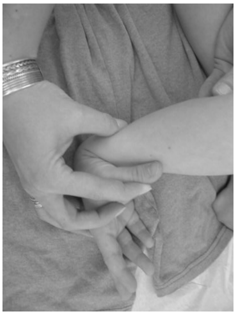

Fig. 17.1 Abnormal contact between the thumb and forearm in a young girl with benign hypermobility joint syndrome.

8. Do children with hypermobility experience pain?

Yes. Hypermobility is a common cause of pain after activity and evening joint pain (intermittent arthralgia). The condition is benign and inconsequential except for the pain experience. Hypermobility is a common finding among school-age and preschool-age children. Most hypermobile children are asymptomatic.

9. Which children can demonstrate a Gorlin sign?

Gorlin sign is the ability to touch the tip of the nose with the tongue. It is seen in conditions associated with hypermobility syndromes, such as Ehlers-Danlos syndrome.

10. In what settings can reactive arthritis occur?

Reactive arthritis in its broadest sense refers to a pattern of arthritis associated with a nonarticular (remote) infection. By definition, it is an inflammatory arthritis, but a live organism cannot be isolated by culture of synovial fluid or synovial biopsy. A restricted definition of the syndrome includes arthritis after enteric (e.g., *Salmonella, Shigella, Yersinia, Campylobacter, Giardia*) or genitourinary infections (e.g., *Chlamydia*).

Schmitt SK. Reactive arthritis. *Infect Dis Clin North Am.* 2017;31(2):265–277.
Morris D, Inman RD. Reactive arthritis: developments and challenges in diagnosis and treatment. *Curr Rheumatol Rep.* 2012;14(5):390–394.

11. What conditions are associated with gastrointestinal symptoms and arthritis?

Noninfectious

- Ulcerative colitis
- Crohn disease
- Behçet disease
- Henoch-Schönlein purpura (HSP)
- Celiac disease

Infectious

- Salmonella
- Shigella

- Yersinia
- Campylobacter
- Clostridium difficile
- Tuberculosis
- Giardiasis

12. One week after mild trauma, an 8-year-old girl has pain and tenderness in the right foot and leg, both of which are cold, exquisitely tender to the touch, with mottled discoloration. What is the likely diagnosis?

Complex regional pain syndrome (CRPS), type 1. Previously called *reflex sympathetic dystrophy* or *reflex neurovascular dystrophy,* this poorly understood entity is often confused with arthritis because of localized severe pain in one of the extremities. Pain is out of proportion to any antecedent history or physical examination. Several features separate it from arthritis. The pain is not confined to a single joint; it is regional in nature, involving portions of an extremity; and it often follows minor trauma (± immobilization or walking aid use). The pain is very severe, and even light touch causes pain (i.e., hyperesthesia). Several dysautonomic changes (e.g., mottling, color changes, sweating, edema) may occur but not always. Laboratory findings are normal, including inflammatory markers. Imaging techniques or nerve conduction studies are not needed unless the diagnosis is in question. Regional osteopenia as a result of disuse may develop in very severe cases.

Because the role of the sympathetic nervous system is unclear and dystrophy may not occur in all cases, the terminology change has been revised by the International Association for the Study of Pain. In *type 1,* all of the features of the complex are present without definable nerve injury. In *type 2,* a definable nerve injury is present. The vast majority of children have type 1.

Stanton-Hicks MD. CRPS: What's in a name? Taxonomy, epidemiology, neurologic, immune and autoimmune considerations. *Reg Anesth Pain Med.* 2019;44(3):376–387.

International Association for the Study of Pain. Complex regional pain syndromes. www.iasp-pain.org. Accessed January 25, 2020.

13. How is CRPS managed?

Although many children are casted because of suspected hairline fractures, immobilization is contraindicated. Treatment is aimed at providing pain relief using analgesics and other nonmedical modalities. It is important that families be given a good explanation of the mechanism of pain and assurance that this condition is controllable. A physical therapy program should be started immediately, with emphasis on passive and active range-of-motion exercises and the maintenance of function and pain desensitization. Aquatic therapy is particularly useful in these children to initiate therapy. Desensitization of the painful area using one of several modalities (e.g., biofeedback, transcutaneous electrical nerve stimulation, visualization, acupuncture) can be part of the program. A positive attitude on the part of physicians and therapists is essential. Therapists treating CRPS should be familiar with this pediatric condition and be skillful in balancing aggressive encouragement to promote limb use and weight bearing without deterring from adherence to the program.

Rabin J, Brown M, Alexander S. Update in the treatment of chronic pain within pediatric patients. *Curr Probl Pediatr Adolesc Health Care.* 2017;47(7):167–172.

Katholi BR, Daghstani SS, Banez GA, et al. Noninvasive treatments for pediatric complex regional pain syndrome: a focused review. *PM&R.* 2014;6(10):926–933.

Lee BH, Scharff L, Sethna NF, et al. Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. *J Pediatr.* 2002;41(1):135–140.

14. Do children develop fibromyalgia?

Children as young as 9 years of age have been diagnosed with this syndrome. *Fibromyalgia* (in children often referred to as *juvenile primary fibromyalgia* or *juvenile-onset fibromyalgia*) is a condition that is characterized by musculoskeletal aches and pains, fatigue, variable disturbed sleep patterns, and tenderness over various parts of the body. These tender points are useful for the diagnosis (Fig. 17.2). There should be tenderness over at least 4 of these 11 points for proper classification of individuals. In addition, there should be no tenderness over nonspecific sites such as the forehead or the pretibial region.

Aches and pains are extremely common in children and may be the result of serious medical diseases (e.g., leukemia), mental illness (e.g., depression), and psychosocial stress. Differentiation of chronic musculoskeletal pain of nonorganic origin may be difficult in children and adolescents.

Criteria for diagnosis of fibromyalgia
(American College of Rheumatology)

1. **History of widespread pain**
   Pain is considered widespread when it occurs on both sides of the body above and below the waist. Axial skeletal pain must be present.
2. **Pain in 11 of 18 bilateral tender point sites on digital palpation**
   (using about 4 kg of pressure).

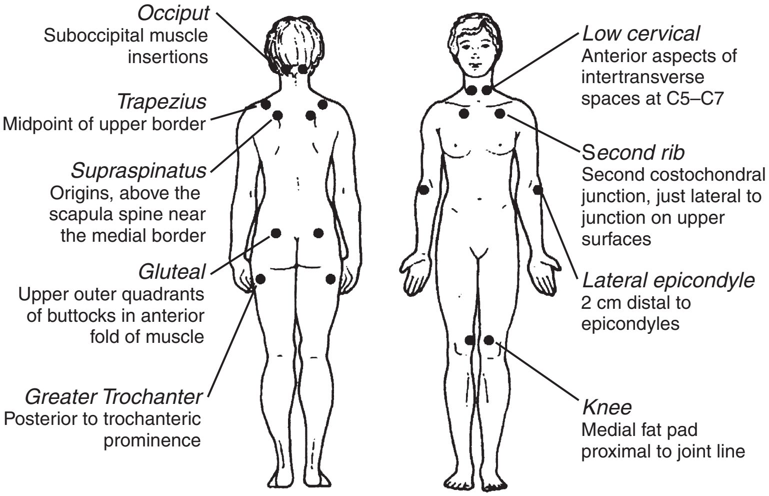
Occiput
Suboccipital muscle insertions
Trapezius
Midpoint of upper border
Supraspinatus
Origins, above the scapula spine near the medial border
Gluteal
Upper outer quadrants of buttocks in anterior fold of muscle
Greater Trochanter
Posterior to trochanteric prominence
Low cervical
Anterior aspects of intertransverse spaces at C5–C7
Second rib
Second costochondral junction, just lateral to junction on upper surfaces
Lateral epicondyle
2 cm distal to epicondyles
Knee
Medial fat pad proximal to joint line

Fig. 17.2 American College of Rheumatology criteria for the diagnosis of fibromyalgia. (From Ballinger S, Bowyer S. Fibromyalgia: the latest "great" imitator. *Contemp Pediatr.* 1997;14:147.)

15. What is the presumed pathogenesis of fibromyalgia?

The pathogenesis is poorly understood, but fibromyalgia appears to be a disorder of pain regulation with dysfunctionality of normal ascending and descending pain processes and increased central sensitivity to pain. There is likely a complex interaction of **genetic** (e.g., strong association among family members), **neurobiologic** (e.g., abnormalities in neurotransmitters), **neurohormonal** (e.g., abnormalities of the hypothalamic–pituitary axis), and **environmental** (e.g., maladaptive stress responses) factors.

Chinn S, Caldwell W, Gritsenko K. Fibromyalgia pathogenesis and treatment options update. *Curr Pain Headach Rep.* 2016;20(4):25.

DERMATOMYOSITIS AND POLYMYOSITIS

16. What criteria are used for the diagnosis of juvenile dermatomyositis and polymyositis?

- Symmetric proximal muscle weakness (e.g., Gowers sign)
- Elevated serum enzymes in muscle (creatine kinase [CK], lactic dehydrogenase [LDH], aspartate transaminase [AST], and/or aldolase]
- Abnormal electromyogram (increased insertional activity, myopathic pattern, polymorphic potentials)
- Inflammation and/or necrosis on muscle biopsy
- Characteristic skin eruption

The *presence of rash* distinguishes dermatomyositis from polymyositis. Three out of four criteria plus a pathognomonic rash establish the diagnosis of dermatomyositis, and confirmatory biopsy is not necessary. If fewer criteria are met, a biopsy may be needed for diagnosis. New diagnostic criteria developed by the American College of Rheumatology in 2017 take the form of a weighed point score. The value of the muscle biopsy was heightened by these new criteria.

Vehe RK, Riskalla MM. Collagen vascular diseases: SLE, dermatomyositis, scleroderma, and MCTD. *Pediatr Rev.* 2018;39(10):501–515.
Lundberg IE, Tjarnlund A, Bottai M, et al. European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis.* 2017;76(12):1955–1964.

17. What skin changes are pathognomonic for dermatomyositis?

Gottron patches (Fig. 17.3). These begin as inflammatory papules over the dorsal aspect of interphalangeal joints (knuckles), along the sides of the fingers, and on the extensor aspect of the elbows and knee joints. The papules become violaceous and flat topped and may coalesce to become patches. Eventually, the lesions show atrophic changes and become hypopigmented.

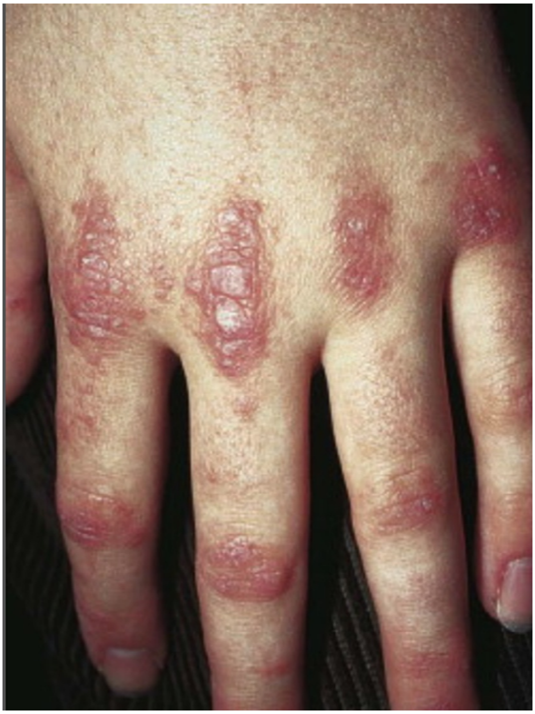

Fig. 17.3 Gottron papules. (From Cohen BA. *Pediatric Dermatology.* 4th ed. Philadelphia, PA: Elsevier; 2013:200.)

18. What are the other classic cutaneous findings of dermatomyositis among children?

- Periorbital edema and erythema with violaceous color of the upper eyelid (heliotrope rash)
- Rash over the upper chest in the shawl distribution
- Photosensitivity
- Cutaneous vasculopathy with ulceration
- Nail-fold capillary abnormalities

19. Which infectious agents are known to cause myositis?

- **Viral:** Notably coxsackie (named after Coxsackie, New York) and influenza A and B
- **Bacterial:** *Staphylococcus* and *Yersinia* (causing pyomyositis)
- **Protozoal:** *Toxoplasma* and trichinosis
- **Spirochetal:** *Borrelia*

The most common cause of acute muscle disease associated with pain, difficulty walking, and a high level of CK is *viral myositis*.

JUVENILE IDIOPATHIC ARTHRITIS

20. Why did juvenile rheumatoid arthritis (JRA) become JIA?

The Europeans and Canadians have never liked the term *rheumatoid* embedded in JRA, which has been used in the United States since 1977, because it suggests homology with the adult disease (rheumatoid arthritis). In the same year of 1977 in the city of Basel, European investigators coined the term juvenile *chronic* arthritis (JCA), which included pretty much all forms of primary childhood arthritis. The International League of Associations of Rheumatology (ILAR) ended the transatlantic dispute and came up with the new name—JIA. At least there is some consistency because the “J” and the “A” remain unchanged. “J” stands for *juvenile* (before the seventeenth birthday for disease onset), and “A” for *arthritis,* meaning joint inflammation. The new classification went through multiple revisions and is still a work in progress. The potential advantages are (1) an end to the confusion and (2) the hopeful beginning of a solution by at least recognizing that we do not know what causes the disease (it may pay to be humble).

21. What is synovitis, and at what point is it considered chronic?

Synovial inflammation (synovitis) is the primary pathologic lesion in JIA. It is chronic at 6 weeks.

22. What is the most common chronic arthritis seen in children?

JIA, with a point prevalence of about 1:1000.

23. What are the diagnostic criteria for the classification of JIA?

JIA is a *diagnosis of exclusion*. Features include the following:

- Onset at $\leq$16 years of age
- Clinical arthritis with joint swelling or effusion, increased heat, and limitation of range of motion with tenderness
- Duration of disease of $\geq$6 weeks

24. What are the seven main subsets of JIA?

The seven major subgroups are distinguished by the number of joints, presence of rheumatoid factor, and different combination of extra-articular manifestations (Table 17.1).

Table 17.1 Subsets of Juvenile Idiopathic Arthritis

SUBSET	NO. OF JOINTS	AGE	UVEITIS	RF	ANA	HLA-B27	REMISSION	OTHER SYMPTOMS
Systemic	Any	0-16 mo	—	—	—	—	50%	Fever, visceromegaly, serositis, rash
Oligopersistent	1-4	2 yr	++++	—	++++	—	60%	None
Oligoextended[*]	>5	2 yr	++++	—	++++	—	20%	None
Polyarticular RF(−)	>5	3 yr	+++	—	+++	—	15%	Subcutaneous nodules (small)
Polyarticular RF(+)	>5	12-17 yr	None	+	++	—	0%	Subcutaneous nodules (large)
Enthesitis-related arthritis	Any number	8-16	Acute	—	—	+	Unknown	Tendinous involvement Enthesitis[†]
Psoriatic arthritis	Any number	Any	+	—	+/−		Low	Dactylitis, psoriasis of nails and skin, tendinous involvement
Other arthritis[‡]		N/A	N/A	N/A	N/A	N/A	N/A	N/A

[*] After a typical oligoarticular onset with an oligoarticular course for 6 months, the new joints become recruited.
[†] Inflammation at the insertion point of tendons, capsule, and ligaments.
[‡] Any form of chronic arthritis that fails to meet criteria for any of the other subsets.
ANA, Antinuclear antibody; *HLA,* human leukocyte antigen; *RF,* rheumatoid factor.

25. What percentage of pediatric JIA presents as systemic JIA (sJIA)?

Five percent to 15% of JIA present as systemic in North America and Europe. In Asia, however, sJIA appears to account for a greater percentage of JIA cases, with 25% in India and 50% in Japan.

26. What is the pattern of fever and characteristic rash of sJIA?

Affected individuals with sJIA typically have a fever of unknown origin with once- or twice-daily (i.e., quotidian) temperature spikes, often higher than 104°F (40°C). Shaking chills often precede the fever. The temperature characteristically returns to 98.6°F (37°C) or lower; continuous fever should suggest other diagnoses. A blotchy, light pink, evanescent rash that blanches on compression and that may show perimacular pallor accompanies the fever in more than 90% of cases (Fig. 17.4). The rash of sJIA is diagnostic only after the diagnosis is made (by exclusion). Arthritis may not be present during the first several weeks of illness. Serositis, hepatosplenomegaly, and lymphadenopathy are other significant findings in patients with this form of the disease.

Lee JJY, Schneider R. Systemic juvenile idiopathic arthritis. *Pediatr Clin North Am.* 2018;65(4):691–709.

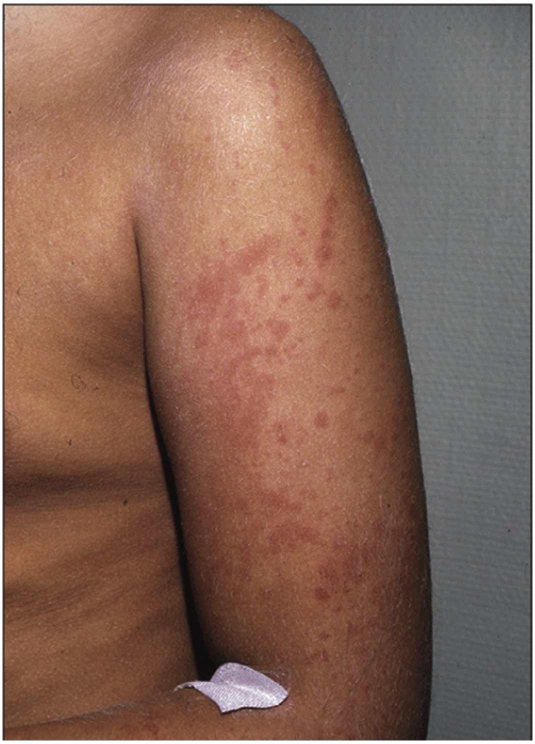

Fig. 17.4 Typical rash of systemic-onset juvenile rheumatoid arthritis. (From Hochberg MC, Gravallese EM, Silman AJ, et al, eds. *Rheumatology.* 7th ed. Philadelphia, PA: Elsevier; 2019:882.)

27. In addition to different clinical features, how is sJIA distinguished from other subgroups of JIA?

- Equal sex distribution (other subgroups more commonly occur in females)
- Rarely familial
- Lack of autoantibodies (e.g., rheumatoid factor, ANA) and autoreactive T cells
- Lack of human leukocyte antigen (HLA) associations
- Greater responsiveness to interleukin-1 (IL-1) and interleukin-6 (IL-6) inhibition
- Autoinflammatory, rather than autoimmune, disease (see question 107)

Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet.* 2011;377:2138–2149.

28. Why is it sometimes difficult to distinguish sJIA from leukemia?

Up to 20% of patients with acute lymphoblastic leukemia (ALL) have some degree of musculoskeletal symptoms, including joint pain and occasional swelling, that can mimic sJIA. In both diseases, there is anemia, fever, and weight loss. Both can involve hepatosplenomegaly and lymphadenopathy. In ALL, however, the fever is not usually spiking, and platelets and white blood cell counts tend to be low to low normal. In ALL compared with sJIA, pain occurs more commonly at nighttime. A good examination of a peripheral smear is crucial. More than one bone marrow biopsy may be necessary.

Marwaha RK, Kulkarni KP, Bansal D, Trehan A. Acute lymphoblastic leukemia masquerading as juvenile rheumatoid arthritis: diagnostic pitfall and association with survival. *Ann Hematol.* 2010;89(3):249–254.

Jones OY, Spencer CH, Bowyer SL, et al. A multicenter case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. *Pediatrics.* 2006;117(5):e840–e844.

29. In a patient with suspected rheumatic disease, what clinical features are more suggestive of malignancy?

Particularly concerning are **nonarticular bone pain** and **back pain** as the principal symptomatic features, **bone tenderness**, and **severe constitutional symptoms**. Children with rheumatic joint problems are typically stiff, and they may complain about pain. The pain of malignancy is out of proportion to the amount of swelling around the joint, and it tends to be worse at night. It is vital to think about the possibility of malignancy in children with rheumatic complaints.

Cabral DA, Tucker LB. Malignancies in children who initially present with rheumatic complaints. *J Pediatr.* 1999;134(1):53–57.

30. What is the value of measuring ANA and rheumatoid factor (RF) in patients with JIA?

After JIA has been diagnosed on clinical grounds, results of these tests help assign the patient to the appropriate category (e.g., oligoarticular or RF-positive polyarticular). These tests are also useful as prognostic indicators. Because ANA can be present in 10% to 30% of normal children, this test should not be used as a screening test to diagnose JIA in children who experience noninflammatory pain. The presence of ANA increases the risk for uveitis, thereby making ophthalmologic surveillance more important. RF is valuable as a marker of poor functional prognosis in adolescents with polyarticular arthritis.

31. Are radiographs helpful for diagnosing JIA?

No. There are no characteristic radiographic changes at onset. The value of radiology is to rule out other skeletal conditions and to provide a documented baseline status of joint integrity.

32. A patient with sJIA who becomes ill with thrombocytopenia, profound anemia, and markedly elevated transaminases probably has what complication?

Macrophage activation syndrome (MAS). This new conceptualization of an old problem is seen in children with sJIA both at onset (even at presentation) and late during the course of disease. It is characterized by excessive immune activation with massive upregulation of T-cell and macrophage function, with vast release of proinflammatory cytokines leading to *hemophagocytosis* (the hallmark, yet not necessary for diagnosis). It is believed that in most cases, MAS is triggered by a viral infection (with Epstein-Barr virus [EBV] being the most common culprit). MAS is the single most important contributor of mortality, together with gastrointestinal bleeding and infection, among patients with sJIA.

Cron RQ, Davi S, Minoia F, Ravelli A. Clinical features and correct diagnosis of macrophage activation syndrome. *Expert Rev Clin Immunol.* 2015;11(9):1043–1053.

Bennett TD, Fluchel M, Hersh AO, et al. Macrophage activation syndrome in children with systemic lupus erythematosus and children with juvenile idiopathic arthritis. *Arthritis Rheum.* 2012;64(12):4135–4142.

33. What are the main features of MAS?

- Worsening of fever and rash
- Anemia, frequently severe (due in part to hemophagocytosis), leukopenia, and thrombocytopenia
- Hypofibrinogenemia and pseudonormalization of ESR (due to low fibrinogen)
- Liver dysfunction
- Hypertriglyceridemia
- Hyponatremia
- Massive increase in ferritin levels
- Occasional central nervous system (CNS) involvement
- Generalized musculoskeletal pain

Davi S, Consolaro A, Guseinova D, et al. An international consensus survey of diagnostic criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis. *J Rheumatol.* 2011;38(4):764–768.

KEY POINTS: JUVENILE IDIOPATHIC ARTHRITIS

1. *Sine qua non*: Persistence for $\geq$6 weeks
2. Seven subtypes differentiated by number of involved joints, presence of RF, and extra-articular involvement
3. Characteristic finding: Morning stiffness or soreness that improves during the day
4. No laboratory tests are diagnostic.
5. Patients $<$7 years old with ANA-positive oligoarticular JIA at highest risk for uveitis

34. What is the traditional first-line approach to medical management of JIA?

The so-called first-line therapy consists of **nonsteroidal anti-inflammatory drugs (NSAIDs)**. Given at the correct dose, they exert pain relief and suppress inflammation (decrease in morning stiffness), with a peak action at 4 to 6 weeks. The classic members of this group are aspirin, ibuprofen, naproxen, tolmetin, and indomethacin. Choice among them is made on the basis of availability in liquid form, half-life, side-effect profile, individual doctor preferences, and results of an individual trial. Most of their action is through inhibition of cyclooxygenase. About one-third of patients have their symptoms controlled through the use of NSAIDs; two-thirds require more aggressive drug therapy. For patients with oligoarticular disease, intra-articular injection of corticosteroids is also considered first-line therapy.

35. What second-line agents have been used historically in the treatment of JIA?

- Gold salts
- Penicillamine
- Hydroxychloroquine
- Sulfasalazine
- Methotrexate

Of these, only methotrexate has been proved beneficial in a randomized, double-blind, placebo-controlled trial.

Giancane G, Consolaro A, Lanni S, et al. Juvenile idiopathic arthritis: diagnosis and treatment. *Rheumatol Ther.* 2016;3(2):187–207.

Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis: results of the USA-USSR double blind placebo controlled trial. *N Engl J Med.* 1992;326(16):1043–1049.

36. When are corticosteroids indicated for children with JIA?

- Life-threatening disease (e.g., pericarditis, myocarditis)
- Unremitting fever not responsive to NSAIDs
- Unrelenting polyarthritis with severe limitations requiring intensive physical therapy to achieve ambulatory status
- Topical therapy for uveitis (systemic steroids are sometimes needed for children with aggressive uveitis unresponsive to topical therapy)
- As intra-articular injections to treat unresponsive joints or single joint disease in the context of intolerance to or lack of efficacy of NSAIDs. Triamcinolone hexacetonide is the drug of choice.

37. What are the most common side effects of prolonged corticosteroid therapy?

Effects can be minimized by alternate-day therapy, but sometimes the treatment is worse than the disease. Commonly encountered problems associated with high-dose corticosteroid use in children can be remembered using the mnemonic **CUSHINGOID MAP**:

- **C**ataracts
- **U**lcers
- **S**triae
- **H**ypertension
- **I**nfectious complications
- **N**ecrosis of bone (avascular)
- **G**rowth retardation
- **O**steoporosis
- **I**ncreased intracranial pressure (pseudotumor cerebri)
- **D**iabetes mellitus
- **M**yopathy
- **A**dipose tissue hypertrophy (obesity, "buffalo hump")
- **P**ancreatitis

38. What are biologic agents?

These are genetically engineered products that act by blocking specific immune pathways, such as cytokine signaling, to lessen inflammation. Etanercept, the first biologic agent used in the treatment of JIA, blocks the actions of tumor necrosis factor-α (TNF-α), a proinflammatory cytokine. A growing variety of other agents are used, including adalimumab, another antibody to TNF, and abatacept, which is a costimulation blocker that acts by blocking receptors on antigen-presenting cells. Adalimumab is the only biologic agent with proven efficacy to treat uveitis. Newer biologics have been developed to control upregulated IL-1 (anakinra, rilonacept, and canakinumab) and IL-6 (tocilizumab). Canakinumab is approved for the treatment of systemic-onset JIA and tocilizumab for both systemic and polyarticular JIA. Biologic agents have become important therapeutic options for patients with JIA resistant to or intolerant of conventional treatments.

Vanoni F, Minoia F, Malattia C. Biologics in juvenile idiopathic arthritis: a narrative review. *Eur J Pediatr.* 2017;176(9):1147–1153.

Sen ES, Ramanan AV. New age of biological therapies in paediatric rheumatology. *Arch Dis Child.* 2014;99(7):679–685.

39. Which children with JIA require the most frequent monitoring for uveitis?

Uveitis (also called *iridocyclitis*) is inflammation of the iris and the ciliary body. It occurs, on average, in 20% of patients with **pauciarticular JRA** and in 5% of patients with **polyarticular disease**. Table 17.2 summarizes the American Academy of Pediatrics (AAP) guidelines for the frequency of slit-lamp examination developed by the sections of ophthalmology and rheumatology. Patients at high risk require quarterly examinations; those at moderate risk need biannual examinations; those at low risk can be examined annually.

Clarke S, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Pediatr Rheumatol Online J.* 2016;14(1):27.

Table 17.2 Frequency of Ophthalmologic Examination in Patients With JIA

TYPE	ANTINUCLEAR ANTIBODIES	AGE AT ONSET	DURATION OF DISEASE (YEARS)	RISK CATEGORY	EYE EXAMINATION FREQUENCY (MONTHS)
Oligo- or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	N/A	Low	12
Systemic disease (fever, rash)	N/A	N/A	N/A	Low	12

JIA, Juvenile idiopathic arthritis.

Data from Cassidy J, Kivlin J, Lindsley C, Nocton J. Ophthalmologic examinations in children with juvenile rheumatoid arthritis, *Pediatrics*. 2006;117(5):1843–1845.

40. What is the earliest sign of uveitis among patients with JIA?

When the anterior chamber of the eye is examined with a slit lamp, a "**flare**" is the earliest sign. This is a hazy appearance as a result of an increased concentration of protein and inflammatory cells. Later signs can include a speckled appearance of the posterior cornea (as a result of keratic precipitates), an irregular or poorly reactive pupil (as a result of synechiae between the iris and lens), band keratopathy, and cataracts (Fig. 17.5).

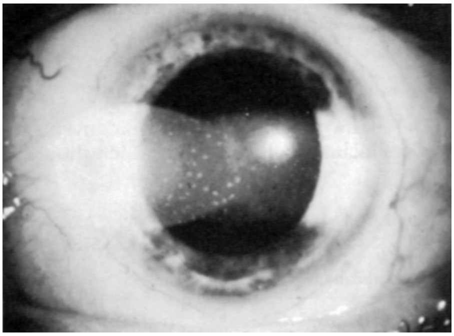

Fig. 17.5 Uveitis. A slit-lamp examination shows "flare" in the fluid of the anterior chamber (caused by increased protein content) and keratic precipitates on the posterior surface of the cornea, representing small collections of inflammatory cells). (From Cassidy JT, Laxer RM, Petty RE, Lindsley CB, eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia, PA: Saunders; 2011:305–314.)

41. What are the juvenile spondyloarthropathies under the revised classification system?

The *spondyloarthropathies* are now considered one of the subsets of JIA and are recognized under the heading **enthesitis-related arthritis (ERA)**.

Adrovic A, Barut K, Sahin S, Kasapcopur O. Juvenile spondyloarthropathies. *Curr Rheumatol Rep.* 2016;18(8):55.

42. What are the characteristic clinical features of the juvenile spondyloarthropathies?

- Affect males >8 years of age
- Enthesitis (inflammation of tendon, capsule, and ligament insertion sites) is characteristic
- Prodromal oligoarthritis involving large joints of the lower extremities, including the hip
- Involvement of the sacroiliac joints and the back, which is manifested as pain, stiffness, and reduced range of motion (Fig. 17.6)
- Associated with HLA-B27 (≤90% in children with ankylosing spondylitis and 60% of those with other spondyloarthropathies)
- Seronegativity: ANA and RF typically negative

Weiss PF, Colbert RA. Juvenile spondyloarthritis: a distinct form of juvenile arthritis. *Pediatr Clin North Am.* 2018;65(4):675–690.

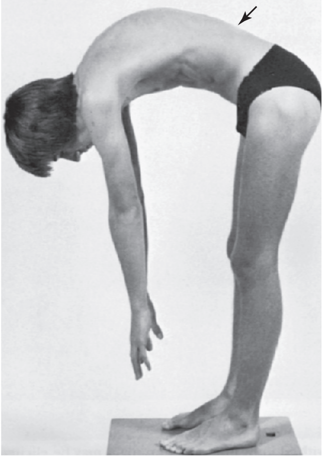

Fig. 17.6 Fifteen-year-old boy shown in the position of maximal forward flexion. Note the flattened back *(arrow).* Radiographs demonstrated bilateral sacroiliac arthritis but no abnormality of the lumbosacral spine. (From Casssidy JT, Laxer RM, Petty RE, Lindsley CB, eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia, PA: Saunders; 2011:272–286.)

43. How is enthesitis diagnosed clinically?

The *enthesis* is the site of attachment of ligaments, tendons, capsule, and fascia to bone. Enthesopathy is unique to the spondyloarthropathies and appears as painful, localized tenderness at the tibial tubercle (which may be mistaken for Osgood-Schlatter disease), the peripheral patella, and the calcaneal insertion of the Achilles tendon (Fig. 17.7) and plantar fascia (which may be mistaken for Sever disease). Thickening of the Achilles tendon and tenderness of the metatarsophalangeal joints are associated findings. Magnetic resonance imaging (MRI) can be

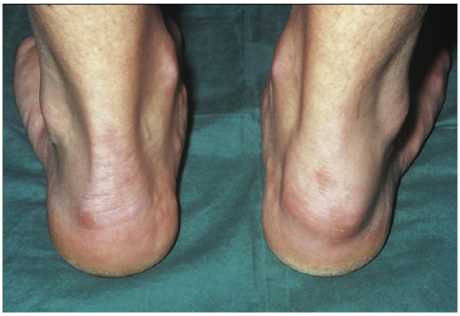

Fig. 17.7 Enthesitis at the insertion of the right Achilles tendon. (From Hochberg MC, Gravallese EM, Silman AJ, et al, eds. *Rheumatology.* 7th ed. Philadelphia, PA: Elsevier; 2019:1003.)

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extremely helpful. The T2-weighted (T2W) image or the short T1 inversion recovery (STIR) sequence may show bone marrow edema adjacent to the enthesis.

44. Why is the diagnosis of ankylosing spondylitis difficult to make in children?

A child may have undifferentiated spondyloarthritis (an enthesitis-related arthritis) that is characterized by enthesitis and recurrent episodes of lower-extremity oligoarthritis for several years before he or she develops back symptoms. To fulfill the criteria for ankylosing spondylitis, clinical features of lumbar spine pain, limitation of lumbar motion, and radiographic signs of sacroiliitis must be present. The average time from onset of symptoms to diagnosis in an adult with ankylosing spondylitis is 5 years; many adolescents are adults before they fulfill the criteria. MRI (STIR or T2W) is very helpful to document early sacroiliitis. For sacroiliitis, no gadolinium is necessary.

45. Where are the dimples of Venus?

The *dimples of Venus* are used to define a baseline for the Schober test. The dimples are **prominent paravertebral indentations in the lower back** of some individuals. A line drawn between the dimples marks the lumbosacral junction, and this is the point from which one measures 10 cm above for an upper limit and 5 cm below for the lower limit to assess anterior flexion of the lumbosacral spine. After the patient bends over without flexing the knees, one takes a second measurement of the distance. The change in length between the upper and the lower point should be now $>$5 cm from the baseline measurement.

LYME DISEASE

46. What criteria are used to diagnose Lyme disease?

Classification criteria (i.e., case definition) as determined by the Centers for Disease Control and Prevention include the following:

- **Erythema migrans:** enlarging circular erythematous lesion (minimum size, 5 cm), *or*
- **At least one clinical manifestation** (arthritis, cranial neuropathy, atrioventricular block, aseptic meningitis, radiculoneuritis) and **isolation or serologic evidence** of *Borrelia burgdorferi* infection

47. What is the typical rash seen in Lyme disease?

The classic rash of **erythema migrans (EM)**, believed to be pathognomonic for Lyme disease, is an expanding erythematous skin lesion (round or oval; $\geq$5 cm) that begins as a small macule or papule at the bite site. As the lesion expands over days to weeks, central or paracentral clearing gives the lesion an annular or target-like appearance (Fig. 17.8). However, EM is not always classic. About 60% of cases have homogenous erythema, 30% with central erythema, 9% with central clearing, 7% with central vesicles or ulcerations, and 2% with central purpura.

Bush LM, Vazquez-Pertego MT. Tick borne illness—Lyme disease. *Dis Mon.* 2018;64(5):195–212.
Dandache P, Nadelman RB. Erythema migrans. *Infect Dis Clin North Am.* 2008;22:235–260.

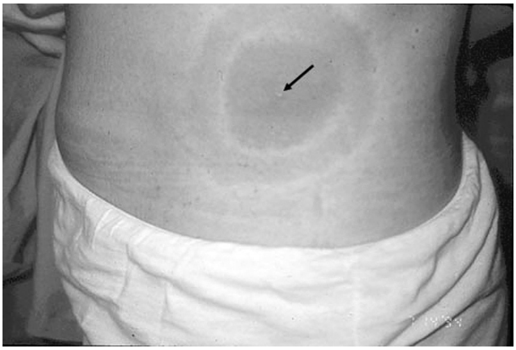

Fig. 17.8 Erythema migrans (EM) with punctum *(arrow)*. (From Dandache P, Nadelman RB. Erythema migrans. *Infect Dis Clin North Am.* 2008:22:237.)

48. How long after a tick bite does the rash of Lyme disease appear?

Median time is **7 to 10 days**, but the rash can appear with a range of 1 to 36 days.

49. How is Lyme disease confirmed in the laboratory?

Although attempts to demonstrate borrelial DNA in infected tissues by polymerase chain reaction has met with some success and cultures occasionally render positive results, the main diagnostic tool continues to be **serology**. Immunoglobulin M (IgM) peaks about 4 weeks after infection, and immunoglobulin G (IgG) peaks at 6 weeks. This is the main reason why antibodies may not be detected during the early dermatologic and neurologic stages.

There are two detection techniques: **ELISA** and **Western blot**. Both are available for IgG and IgM. ELISA measures whole components of *Borrelia*. It is a very sensitive test but with many false-positive results. A negative ELISA requires no further investigation. All positive ELISAs—particularly those with borderline positivity—should be confirmed by Western blot. This is the so-called *two-tier system*. The **C6 peptide ELISA** measures IgG to a relatively invariant lipoprotein on the spirochete, and as a single test has been shown to be as sensitive and almost as specific as the two-tier system. Next-generation serologic assays, using recombinant proteins or synthetic peptides, are currently under study.

Branda JA, Body BA, Boyle J, et al. Advances in serodiagnostic testing for Lyme disease are at hand. *Clin Infect Dis.* 2018;66(7):1133–1139.

Theel ES. The past, present, and (possible) future of serologic testing for Lyme disease. *J Clin Microbiol.* 2016;54(5):1191–1196.

50. If infection ensues after a tick bite, how does Lyme disease progress?

- **Early localized disease:** *2 to 30 days*. Sixty percent to 80% of children will develop EM. Some may have a flulike illness with fever, myalgia, headache, fatigue, arthralgia, and malaise.
- **Early disseminated disease:** *3 to 12 weeks*. Clinical manifestations reflect hematogenous spread to other sites; these include secondary EM (multiple lesions), cranial nerve palsies (primarily facial nerve), and aseptic meningitis. Much more rarely seen in children (compared with adults) are radiculoneuritis and carditis (with varying degrees of heart block).
- **Late disease:** *2 to 12 months*. In children, the most common manifestation is arthritis. Rarely, encephalomyelitis can develop. There is controversy regarding the concept of "chronic Lyme disease," a term used to characterize persistent nonspecific symptoms of headache, fatigue, and arthralgias, which occur after antibiotic treatment. Most infectious disease experts believe that the data do not support that prolonged, unexplained symptoms are due to chronic, treatment-refractory infection with *B. burgdorferi*.

Sood SK. Lyme disease in children. *Infect Dis Clin North Am.* 2015;29(2):281–294.

Lantos PM. Chronic Lyme disease. *Infect Dis Clin North Am.* 2015;29(2):325–340.

Oliveira CR, Shapiro ED. Update on persistent symptoms associated with Lyme disease. *Curr Opin Pediatr.* 2015;27(1):100–104.

51. How is the diagnosis of Lyme meningitis established?

The diagnosis is often inexact and is commonly made on the basis of the finding of cerebrospinal fluid (CSF) pleocytosis and the presence of EM and/or positive serology. Both ELISA and Western blot testing may be negative or indeterminate early during the course of infection, when dissemination to the CNS has occurred. Testing of the CSF for demonstration of *B. burgdorferi* DNA by polymerase chain reaction testing is available, but not sensitive enough.

52. How are Lyme disease and viral meningitis clinically differentiated?

Both are predominantly summertime illnesses, but the distinction is critical because Lyme meningitis requires weeks of intravenous antibiotics. In addition to the possible presence of EM, other areas of clinical distinction in patients with signs and symptoms of meningitis include the following:

- **Cranial neuropathy**, especially peripheral seventh-nerve palsy, is strongly suggestive of Lyme meningitis.
- **Papilledema** is more commonly seen in patients with Lyme meningitis.
- **Longer duration** (7 to 12 days versus 1 to 2 days) of symptoms, including headache before lumbar puncture, is more typical of Lyme meningitis.
- **Rash** of EM.
- **Cerebrospinal fluid pleocytosis** should not have more than 10% neutrophils in Lyme meningitis.

Either the rash of EM, papilledema, or a cranial nerve palsy is seen in more than 90% of patients with Lyme meningitis but in almost none with viral meningitis.

Avery RA, Frank G, Glutting, Eppes SC. Prediction of Lyme meningitis in children from a Lyme disease-endemic region: a logistic-regression model using history, physical, and laboratory findings. *Pediatrics.* 2006;117(1):e1–e7.

Shah SS, Zaoutis TE, Turnquist JL, et al. Early differentiation of Lyme from enteroviral meningitis. *Pediatr Infect Dis J.* 2005;24(6):542–545.

53. Should lumbar punctures be done for patients with facial palsy and suspected Lyme disease?

This remains debated because studies in the late 1990s revealed “occult meningitis” (i.e., CSF pleocytosis) in patients without meningeal signs but with Lyme facial palsy. However, the clinical significance of an abnormal CSF is unclear, and there has been no apparent increase in late-stage Lyme disease in those treated with oral antibiotics alone. Consequently, most experts advise no lumbar puncture for suspected or confirmed Lyme facial palsy, unless there is severe or prolonged headache, nuchal rigidity, or other meningeal signs.

54. How is Lyme arthritis differentiated from septic arthritis?

The inflammation generated by Lyme arthritis is significantly less intense than septic arthritis. Lyme arthritis typically involves a single large joint (knee $\geq$90%), range of motion is less limited than septic arthritis, and weight bearing is sometimes possible. On joint aspiration, septic arthritis more typically shows $>$100,000 cells/mL^3. Septic arthritis is more commonly associated with an elevated peripheral white blood cell count and elevated sedimentation rate. However, young children can present with acute Lyme monoarthritis that mimics a septic joint.

Deanehan JK, Kimia AA, Tan Tanny SP, et al. Distinguishing Lyme from septic knee monoarthritis in Lyme disease-endemic areas. *Pediatrics.* 2013;131(3):e695–e701.

Rosé CD, Fawcett PT, Eppes SC, et al. Pediatric Lyme arthritis: clinical spectrum and outcome. *J Pediatr Orthop.* 1994;14(2):238–241.

55. What is the prognosis for children diagnosed with Lyme arthritis?

Multiple studies have shown that the long-term prognosis for treated patients is excellent, with little morbidity. Clinicians should be aware that persistent synovitis after the completion of a single course of 4 weeks of antibiotics is not rare and not the result of antibiotic failure. In fact, up to two-thirds of patients with Lyme arthritis require 3 months to achieve resolution, and 15% have symptoms of their arthritis for more than 12 months.

Smith BG, Cruz AI Jr, Milewski MD, Shapiro ED. Lyme disease and the orthopaedic implications of Lyme arthritis. *J Am Acad Orthop Surg.* 2011;19(2):91–100.

Gerber MA, Zemel LS, Shapiro ED. Lyme arthritis in children: clinical epidemiology and long-term outcome. *Pediatrics.* 1998;102(4 Pt 1):905–908.

56. What should be suspected if a patient with Lyme disease develops fever and chills after starting antibiotic treatment?

Jarisch-Herxheimer reaction. This reaction consists of fever, chills, arthralgia, myalgia, and vasodilation, and it follows the initiation of antibiotic therapy in certain illnesses (most typically syphilis). It is thought to be mediated by endotoxin release as the organism is destroyed. A similar reaction occurs in 40% or less of patients treated for Lyme disease, and it may be mistaken for an allergic reaction to the antibiotic.

57. Should we follow Lyme disease course and response to therapy with titers?

No! As a result of the continued secretion of antibodies by memory cells, serology (particularly as measured with ultrasensitive commercial kits) for both IgM and IgG antibodies may remain positive for up to 10 to 20 years after microbial eradication. The misinterpretation of positive serology as a proxy for active infection is responsible for many unnecessary antibiotic courses in endemic areas.

Kalish RA, McHugh G, Granquist J, et al. Persistence of immunoglobulin M or immunoglobulin G antibody responses after active Lyme disease. *Clin Infect Dis.* 2001;33(6):780–785.

58. Is antibiotic prophylaxis indicated for all tick bites?

Not for all. In most regions, the rate of tick infestation is low, and thus the likelihood of transmission is also low. Even in endemic areas, the risk for Lyme disease to a placebo group in one controlled study after tick bites was only 1.2%. Treating all tick bites with antibiotics is impractical (some children would be on oral antibiotics throughout the summer). Risk is also extremely low if the tick has been attached for $<$36 hours. However, in certain scenarios in hyperendemic areas, the risk for transmission is higher. The Infectious Diseases Society of America recommends prophylaxis with doxycycline if certain conditions are met:

- The attached tick is a deer tick (adult or nymphal *Ixodes scapularis*).
- As estimated by the degree of engorgement or time of exposure, the tick is likely to have been attached $\geq$36 hours.
- Prophylaxis is initiated within 72 hours of tick removal.
- Infection rate of ticks with *B. burgdorferi* is determined to be $\geq$20% (e.g., as seen in portions of New England, Mid-Atlantic states, Minnesota, Michigan, and Wisconsin).
- Doxycycline is not contraindicated.

If these conditions are met, the recommendation is to treat with a single dose of doxycycline: adolescents/adults, 200 mg, and children ($<$45 kg at any age), 4.4 mg/kg up to a maximum dose of 200 mg. Amoxicillin is not recommended due to its shorter half-life and likely requirement for longer therapy.

American Academy of Pediatrics. Lyme disease. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:523.
Warshafsky S, Lee DH, Francois LK, et al. Efficacy of antibiotic prophylaxis for the prevention of Lyme disease: an updated systematic review and meta-analysis. *J Antimicrob Chemother.* 2010;65(6):1137–1144.
Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43(9):1089–1134.

59. What are other means of preventing Lyme disease?

- Avoidance of tick-infested areas
- Use of light-colored, long-sleeved clothing, with pants tucked into sneakers
- Insect repellents (N,N-diethyl-meta-toluamide [DEET]; permethrin)
- "Tick checks" after potential exposures
- Proper tick removal: Pulling straight out, with tweezers close to skin

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Richardson M, Khouja C, Sutcliffe K. Interventions to prevent Lyme disease in humans: a systematic review. *Prev Med Rep.* 2018;13:16–22.
Hayes EB, Piesman J. How can we prevent Lyme disease? *N Engl J Med.* 2003;348(24):2424–2430.

KEY POINTS: LYME DISEASE

1. Spirochete *B. burgdorferi* is the culprit.
2. Only one-third of patients recall the tick bite.
3. The EM rash is virtually diagnostic.
4. ELISA testing has a high false-positive rate; confirm with Western blot analysis.
5. Potential complications include arthritis, aseptic meningitis, cranial nerve palsies, and atrioventricular block.
6. Lyme meningitis (compared with viral meningitis): Cranial neuropathy and papilledema are more common, with longer duration of symptoms before diagnosis.

60. What happened to the Lyme vaccine?

In 1998, the Food and Drug Administration (FDA) approved LYMErix, a recombinant Lyme vaccine, which in clinical trials had reduced new infections in vaccinated adults by nearly 80%. However, 3 years later, the manufacturer voluntarily withdrew the product from the market due to public concerns (unsubstantiated) of vaccine side effects (including autoimmune Lyme arthritis), negative media coverage, and declining sales. There are currently clinical trials underway in Europe involving new Lyme vaccine formulations.

Plotkin SA. Lemons and Lyme. *J Pediatr Infect Dis Soc.* 2018;7(4):267–269.
Nigrovic LE, Thompson KM. The Lyme vaccine: a cautionary tale. *Epidemiol Infect.* 2007;135(1):1–8.

RHEUMATIC FEVER

61. What is acute rheumatic fever (ARF)?

ARF is a postinfectious, immune-mediated, inflammatory reaction that affects the connective tissue of multiple organ systems (heart, joints, CNS, blood vessels, subcutaneous tissue) and that follows infection with certain strains of group A β-hemolytic streptococci (GABHS). The major manifestations are carditis, polyarthritis, chorea, erythema marginatum, and subcutaneous nodules. In the developing world, acute rheumatic fever and rheumatic heart diseases are the leading causes of cardiovascular death during the first five decades of life.

62. What are the major Jones criteria for ARF?

The mnemonic **J ♥ NES** may be useful:

- ***J***_oints_: Migratory arthritis
- **♥**: Heart disease
- ***N***_odules_: Subcutaneous nodules
- ***E***_rythema_: Erythema marginatum
- ***S***_ydenham_: Sydenham chorea

63. What is acceptable proof of antecedent streptococcal pharyngitis when diagnosing ARF?

- **Throat culture:** This is the gold standard for diagnosis of GABHS. Positive cultures, however, do not distinguish GABHS pharyngitis from a carrier state.

- **Streptococcal antigen tests:** Rapid diagnostic tests for the detection of GABHS antigens in pharyngeal secretions are acceptable evidence of infection because they are highly specific. Again, positive tests do not distinguish true infection from a carrier state.
- **Antistreptococcal antibodies:** At the time of clinical presentation with ARF, throat cultures are usually negative. It is reasonable to assess the levels of antistreptococcal antibodies in all cases of suspected rheumatic fever because the antibodies should be elevated at the time of presentation.

Burke RJ, Chang C. Diagnostic criteria of acute rheumatic fever. *Autoimmun Rev.* 2014;13(4–5):503–507.
Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis of acute streptococcal pharyngitis. *Circulation.* 2009;119(11):1541–1551.

64. Which antistreptococcal antibodies are most commonly measured?

The most commonly employed test measures antibodies to **anti-streptolysin O**. The cutoff for a positive test in a school-age child is 320 Todd units (240 in an adult); levels peak 3 to 6 weeks after infection. If the test is negative—as may be the case in ≤20% of patients with ARF and in 40% of those with isolated chorea—other antistreptococcal antibodies may be detected. The most practically available of these identifies antibodies to **deoxyribonuclease B** (positive cutoff, 240 units in children, 120 in adults). Alternatively, subsequent convalescent samples run simultaneously with the acute sample may detect rising titers of either anti-streptolysin O or anti-deoxyribonuclease B.

65. What are the common manifestations of carditis in patients with ARF?

In his *Etudes Médicales du Rhumatisme*, Lasègue remarked that “rheumatic fever licks the joints … and bites the heart,” meaning that the severity of the two manifestations tends to be inversely related. In more recent outbreaks of ARF, ≤80% of patients have had evidence of carditis. ARF causes a pancarditis, which potentially affects all layers (from the pericardium through the endocardium) and may include the following:

- **Valvulitis:** This is heralded by a new or changing murmur. The most common manifestation is isolated mitral regurgitation, and this is followed in frequency by a mid-diastolic rumble of unclear pathophysiology (Carey-Coombs murmur), and then by aortic insufficiency in the presence of mitral regurgitation. Isolated aortic insufficiency is uncommon, and so are stenotic lesions.
- **Dysrhythmias:** Electrocardiogram abnormalities typically involve some degree of heart block.
- **Myocarditis:** When mild, this may manifest as resting tachycardia out of proportion to fever. However, when it is clinically more severe and in combination with valvular damage, myocarditis may lead to congestive heart failure.
- **Pericarditis:** Patients may have chest pain or friction rub. Pericarditis and myocarditis virtually never occur in isolation.

Messeloff CR. Historical aspects of rheumatism. *Med Life.* 1930;37:3–56.

66. How quickly can valvular lesions occur in children with ARF?

New murmurs appear within the first 2 weeks in 80% of patients, and they rarely occur after the second month of illness. Hence, during an episode, one normal echocardiogram in the first 2 weeks should be sufficient to eliminate carditis.

67. What are the typical characteristics of arthritis in patients with ARF?

Migratory polyarthritis is usually the earliest symptom of the disease, and it typically affects the large joints, the knees, the ankles, the elbows, and the wrists (the hips are not commonly involved). The joints can be extraordinarily painful; weight bearing may not be possible. Physical examination discloses warmth, erythema, and exquisite tenderness such that the weight of even bedclothes and sheets may not be tolerable. This tenderness is typically out of proportion with the degree of swelling.

68. What is the effect of aspirin therapy on the arthritis of ARF?

This type of arthritis is exquisitely sensitive to even modest doses of salicylates, which effectively arrest the process within 12 to 24 hours. If aspirin or other NSAIDs are employed early during the course of the condition, the arthritis will not migrate, and a delay in diagnosis may result. Such medications should be withheld until the clinical course of the illness has become clear. Conversely, if there is not a dramatic response to aspirin, a diagnosis other than rheumatic fever should be considered.

69. What is the rash of ARF?

Erythema marginatum. This rash occurs in <5% of cases of ARF. If you see it and call a colleague to the bedside to confirm it, it is likely to have disappeared in the meantime. It is an evanescent, pink to slightly red, nonpruritic eruption with pale centers and erythematous, serpiginous borders; it may be induced by the application of heat, and it always blanches when palpated. The outer edges of the lesion are sharp, whereas the inner borders are diffuse (Fig. 17.9). It is most often found on the trunk and proximal extremities (but not the face). Erythema marginatum is seen almost solely in patients with carditis.

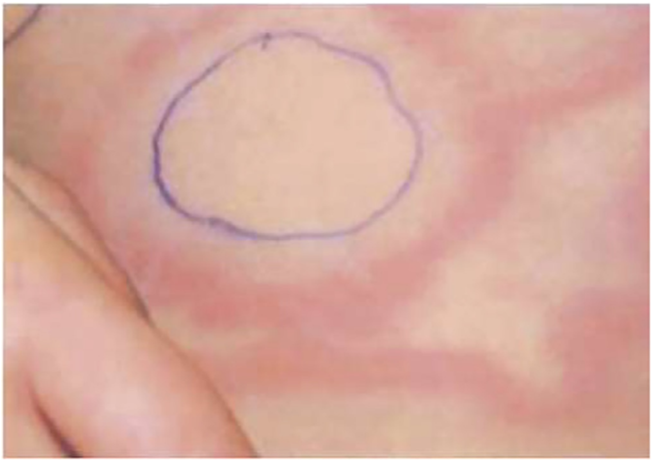

Fig. 17.9 Erythema marginatum demonstrating serpiginous margins and rapid migration: the pen mark shows the location of the rash about 60 minutes earlier. (From Dougherty S, Carapetis J, Zühlke L, et al, eds. *Acute Rheumatic Fever and Rheumatic Heart Disease*. Philadelphia, PA: Elsevier; 2020: 46.)

70. What is Sydenham chorea?

Purposeless, involuntary, irregular movements of the extremities that are associated with muscle weakness and labile emotional behavior. These symptoms are believed to result from inflammation of the cerebellum and of the basal ganglia.

Wei F, Wang J. Sydenham's chorea or St. Vitus's dance. *N Engl J Med.* 2013;369(19):e25.

71. Who was Saint Vitus?

Saint Vitus was a Sicilian youth who was martyred in the year 303 at the age of 14. In the Middle Ages, individuals with chorea would worship at shrines dedicated to this saint. Accordingly, Sydenham chorea is also known as "Saint Vitus dance." Saint Vitus is the patron saint of dancers and comedians. And chorea, by the way, means "dance" in Greek! St. Vitus was one of the 14 Holy Helpers. He was invoked to help people with epilepsy, nervous disorders, and Sydenham chorea, although at the time of Vitus, there was no Sydenham. Thomas Sydenham (the "British Hippocrates") was born in 1624.

72. Are corticosteroids of benefit for the treatment of ARF?

Controlled studies in the 1950s failed to show any definite benefit of corticosteroids for the treatment of rheumatic carditis. Nonetheless, it is generally recommended that patients with severe carditis (e.g., congestive heart failure, cardiomegaly, third-degree heart block) receive prednisone (2 mg/kg per day) in addition to conventional therapy for their heart failure. The unusual patient with well-documented rheumatic arthritis who does not respond to salicylates or NSAIDs will benefit symptomatically from prednisone.

73. Can antibiotic prophylaxis for ARF ever be discontinued?

The optimal duration of antistreptococcal prophylaxis after documented ARF is the subject of some debate. It is clear that the risk for recurrence decreases after 5 years have elapsed from the most recent attack. Most clinicians therefore recommend discontinuing prophylaxis in patients who have not had carditis after 5 years or on the twenty-first birthday (whichever comes later). Those at high risk for contracting streptococcal pharyngitis (e.g., school teachers, health care professionals, military recruits, others living in crowded conditions) and anyone with a history of carditis should receive antibiotic prophylaxis for longer periods. Recommendations vary, ranging from 10 years to the fortieth birthday (whichever is longer) to lifelong prophylaxis, depending on the extent of residual heart disease.

74. Where do PANDAS live in the world of pediatric rheumatology?

In 1989, Swedo and colleagues characterized the psychiatric abnormalities found in children with Sydenham chorea, noting a high prevalence of obsessive-compulsive disorder (OCD) behaviors. They also described a syndrome, which they dubbed **PANDAS** (**p**ediatric **a**utoimmune **n**europsychiatric **d**isorders **a**ssociated with **s**treptococcal infection), in which OCD and Tourette syndrome in some children appeared to be triggered or exacerbated by streptococcal infections in the absence of classic chorea or other manifestations of rheumatic fever. PANDAS has been expanded into **PANS** (**p**ediatric **a**cute-onset **n**europsychiatric **s**yndrome), which theorizes a wider possibility of antecedent triggers for acute OCD symptoms.

The existence of PANDAS (and PANS) remains controversial. There has been no prospective study of group A streptococcal infection to confirm the association of streptococcal pharyngitis with these behavioral abnormalities. The symptoms of tic disorders and OCD tend to fluctuate spontaneously and may be nonspecifically exacerbated by illness. In some cases, the only link to streptococcal infection has been a single throat culture or serologic test, thereby bringing the specificity of the condition into question. PANDAS currently remains an unproven hypothesis.

Chiarello F, Spitoni S, Hollander E, et al. An expert opinion on PANDAS/PANS: highlights and controversies. *Int J Psychiatry Clin Pract.* 2017;21(2):91–98.
Swedo SE, Rapaport JL, Cheslow DL, et al. High prevalence of obsessive-compulsive symptoms in patients with Sydenham chorea. *Am J Psychiatry.* 1989;146(2):246–249.

SYSTEMIC LUPUS ERYTHEMATOSUS

75. What is SLE?

SLE is a multisystem autoimmune disorder characterized by the production of autoantibodies and a wide variety of clinical and laboratory manifestations.

76. What is the origin of the term “lupus” in lupus erythematosus?

Lupus is the Latin word for *wolf.* The term has been used as early as 916 CE to describe erosive facial features similar to those that might result from a wolf’s bite. It was not until the late 1800s that lupus was categorized into discoid (cutaneous, primarily skin involvement) and systemic forms.

Smith CD, Cyr M. The history of lupus erythematosus. From Hippocrates to Osler. *Rheum Dis Clin North Am.* 1998;14(1):1–14.

77. What laboratory tests should be ordered in a child who is suspected of having SLE?

A useful study for SLE is the **ANA** test. Up to 97% of patients with SLE have positive ANAs at some point during their illness. In a patient with characteristic signs and symptoms, a positive ANA may help confirm suspicions of SLE. Unfortunately, however, 10% or more of the normal childhood population may also have a positive ANA. Therefore, a positive ANA in the absence of any objective findings of SLE means very little. Other autoantibodies are much more specific, but they are less sensitive for SLE. These include antibodies to double-stranded DNA and the extractable nuclear antigen Sm. Complement levels are often depressed in patients with active SLE, and sedimentation rates are often elevated. The combination of a positive anti–double-stranded DNA antibody level and a low C_3 level is nearly 100% specific for SLE. Anemia, leukopenia, lymphopenia, and/or thrombocytopenia may also be seen.

Tarvin SE, O’Neil KM. Systemic lupus erythematosus, Sjögren syndrome, and mixed connective tissue disease in children and adolescents. *Pediatr Clin North Am.* 2018;65(4):711–737.
Tsokos GC. Systemic lupus erythematosus. *N Engl J Med.* 2011;365(22):2110–2121.

KEY POINTS: SYSTEMIC LUPUS ERYTHEMATOSUS

1. The hallmark of SLE is the presence of autoantibodies at intermediate to high titers.
2. About 15% to 20% of SLE patients have the onset of disease during childhood.
3. Clinical presentations vary, but the most common presenting symptoms are arthritis, rash, and renal disease.
4. Neonatal SLE is caused by maternal autoantibodies; this leads to complete congenital heart block.
5. The presence of antiphospholipid antibodies predisposes the patient to venous thrombosis.

78. What are the most common manifestations of SLE in children?

- **Arthritis**: 80% to 90%
- **Rash or fever**: 70%
- **Renal disease**, such as proteinuria or casts (every patient with SLE is likely to have some abnormality demonstrated on renal biopsy): 70%
- **Serositis**: 50%
- **Hypertension**: 50%
- **CNS disease** (psychosis/seizures): 20% to 40%
- **Anemia, leukopenia, thrombocytopenia**: 30% each

Thong B, Olsen NJ. Systemic lupus erythematosus diagnosis and management. *Rheumatology (Oxford).* 2017;56(Suppl 1):i1–i13.
Iqbal S, Sher MR, Good RA, Cawkwell GD. Diversity in presenting manifestations of systemic lupus erythematosus in children. *J Pediatr.* 1999;135(4):500–505.

79. Can pancreatitis be a presentation for pediatric SLE?

Yes. Indeed, gastrointestinal manifestations are not uncommon at presentation in pediatric SLE. In many children, lupus presents with atypical features, which may not be part of standardized group classification criteria per either the American College of Rheumatology (ACR) or the Systemic Lupus International Collaborating Clinics (SLICC).

Taddio A, Rossetto E, Rosé CD, et al. Prognostic impact of atypical presentation in pediatric systemic lupus erythematosus: results from a multicenter study. *J Pediatr.* 2010;156(6):972–977.

80. What are the neurologic manifestations of SLE?

Lupus cerebritis is a term that implies an inflammatory etiology of CNS disease. Microscopically, however, widely scattered areas of microinfarction and noninflammatory vasculopathy are seen in brain tissue; actual CNS vasculitis is rarely observed. A lumbar puncture may reveal CSF pleocytosis or an increased protein concentration, but it can be normal as well. Neuropsychiatric manifestations (e.g., psychoses, behavioral changes, depression, emotional lability) or seizures are most commonly observed. An organic brain syndrome with progressive disorientation and intellectual deterioration can be seen. Cranial or peripheral motor or sensory neuropathies, chorea, transverse myelitis, and cerebellar ataxia are less common manifestations of CNS lupus. Severe headaches and cerebral ischemic events have also been seen.

Jeltsch-David H, Muller S. Neuropsychiatric systemic lupus erythematosus: pathogenesis and biomarkers. *Nat Rev Neurol.* 2014;10(10):579–596.

Steinlein MI, Blaser SI, Gilday DI, et al. Neurological manifestations of pediatric systemic lupus erythematosus. *Pediatr Neurol.* 1995;13(3):191–197.

81. Which diseases should be considered in the differential diagnosis of children with a butterfly rash?

A malar rash is present in 50% of children with SLE. The typical butterfly rash involves the malar areas and crosses the nasal bridge, but it spares the nasolabial folds; occasionally, it is difficult to distinguish from the rash of dermatomyositis. See Fig. 17.10. (Erythematous papules on the extensor surfaces of the metacarpophalangeal and proximal interphalangeal joints are common in dermatomyositis, but these are not generally seen in patients with SLE.) Seborrheic dermatitis or a contact dermatitis may be similar to the rash of SLE. Vesiculation should suggest another disease, such as pemphigus erythematosus. Occasionally, children with acne vulgaris may show an erythematous rash in the face that may evoke the butterfly rash. Rosacea is frequently confused with the butterfly rash. A malar flush is clinically distinct and may be seen in children with no disease.

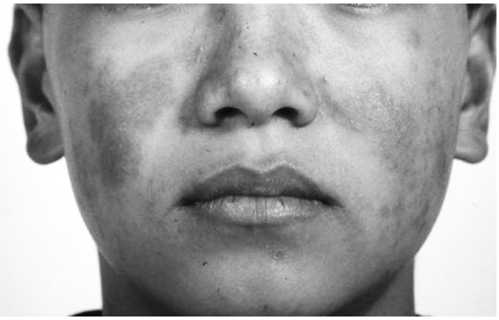

Fig. 17.10 Malar rash of a 14-year-old patient with SLE. The distribution of this typical "butterfly" or malar rash includes the cheeks and crosses the nasal bridge but spares the nasolabial folds. (From Firestein GS, ed. *Kelley's Textbook of Rheumatology.* 9th ed. Philadelphia, PA: Saunders; 2013:1771-1800.)

82. Should children with SLE undergo a renal biopsy?

This is an area of controversy because nearly all children with SLE will have some evidence of renal involvement. Usually, clinical disease (e.g., abnormal urine sediment, proteinuria, renal function changes) correlates with the severity of renal disease on biopsy, but this is not always the case. Extensive glomerular abnormalities can be found on biopsy with minimal concurrent clinical manifestations. For this reason, many authorities are aggressive with early biopsy. Three circumstances in particular warrant biopsy:

- A child with SLE and nephrotic syndrome—to distinguish membranous glomerulonephritis from diffuse proliferative glomerulonephritis (which would warrant more aggressive therapy)

- Failure of high-dose corticosteroids to reverse deteriorating renal function—to determine the likelihood of benefit from cytotoxic therapy
- A prerequisite to entry into clinical therapeutic trials

Silverman E, Eddy A. Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer R, Lindsley C, eds. *Textbook of Pediatric Rheumatology.* 6th ed. Philadelphia, PA: W.B. Saunders; 2011:315–343.

83. How can the result of renal biopsy affect treatment of SLE?

Biopsy can reveal a spectrum of renal pathology, ranging from a normal kidney (rare) to mesangial nephritis or glomerulonephritis (focal or diffuse, proliferative or membranous). Histologic transformation from one group to another over time is not unusual. Treatment of lupus nephritis is based on the severity of the lesion. Mesangial disease may require little or no intervention. Patients with membranous nephropathy commonly have nephrotic syndrome and usually respond to prednisone. Focal proliferative glomerulonephritis is often controlled with corticosteroids alone, but diffuse proliferative glomerulonephritis often requires corticosteroids, intravenous pulse cyclophosphamide, and possibly other immunosuppressives. Among the latter group is mycophenolate mofetil and rituximab (a monoclonal antibody that depletes B cells). Because of the detrimental effects on fertility observed with cyclophosphamide, many investigators feel that mycophenolate should be used instead of cyclophosphamide (including children with diffuse proliferative glomerulonephritis).

Wenderfer SE, Eldin KW. Lupus nephritis. *Pediatr Clin North Am.* 2019;66(1):87–99.

84. When should high-dose corticosteroid therapy be considered for SLE management?

High-dose corticosteroids usually consist of either intravenous pulse methylprednisolone (30 mg/kg per dose with a maximal dose of 1 g given daily or on alternate days given as an intravenous bolus for up to three doses) or oral prednisone. Often, intravenous pulses are then followed by high-dose oral steroids. The main indications for high-dose steroids in cases of SLE are as follows:

- Lupus crisis (widespread acute multisystem vasculitic involvement)
- Worsening CNS disease (as long as steroid psychosis is not thought to be the etiology)
- Severe lupus nephritis
- Acute hemolytic anemia
- Acute pleuropulmonary disease

85. What is the association of antiphospholipid antibodies and lupus?

Antiphospholipid antibodies can cause **recurrent arterial and/or venous thromboses** (e.g., stroke, phlebitis, renal vein thrombosis, placental thrombosis leading to fetal demise). Antiphospholipid antibodies are usually detected as anticardiolipin antibodies or lupus anticoagulant. These antibodies are often seen in patients with SLE, but their prevalence among patients with pediatric lupus varies widely (30% to 87% for anticardiolipin antibodies and 6% to 65% for lupus anticoagulant), depending on the study cited. The pathogenesis of thrombosis in patients with antiphospholipid antibodies remains unclear.

Pons-Estel, Andreoli L, Scanzi F, et al. The antiphospholipid syndrome in patients with systemic lupus erythematosus. *J Autoimmun.* 2017;76:10–20.

Von Scheven E, Athreya BH, Rosé CD, et al. Clinical characteristics of antiphospholipid antibody syndrome in children. *J Pediatr.* 1996;129:339–345.

86. Which laboratory tests are useful for monitoring the effectiveness of therapy in patients with SLE?

Serologic studies can provide useful information about the activity of SLE. The ANA titer does not correlate with disease activity. However, anti–double-stranded DNA titers (if present) often drop, and **complement levels** may increase and return to normal with effective therapy. **Sedimentation rates** usually decrease, and **complete blood cell counts** may return to normal (or at least improve) with effective therapy and decreased disease activity.

87. Can a child with discoid lupus develop systemic lupus?

Discoid lupus, rare in children, is more properly referred to as *cutaneous lupus erythematosus* (CLE) with three main types—acute, subacute, chronic—and these can be further subclassified based on clinical and histologic features. CLE can present as an isolated finding or as a manifestation of underlying SLE. The term *discoid lupus erythematosus* (DLE) specifically refers to a form of chronic CLE in which a patient has well-circumscribed, elevated, red-purplish plaques that have adherent scales, usually on the face (Fig. 17.11). DLE is more commonly found as a manifestation of underlying SLE in children, but if isolated and not systemic, up to one-third of patients may progress to SLE in months or in up to 10 or more years.

Arkin LM, Ansell L, Rademaker A, et al. The natural history of pediatric-onset discoid lupus erythematosus. *J Am Acad Dermatol.* 2015;72(4):628–633.

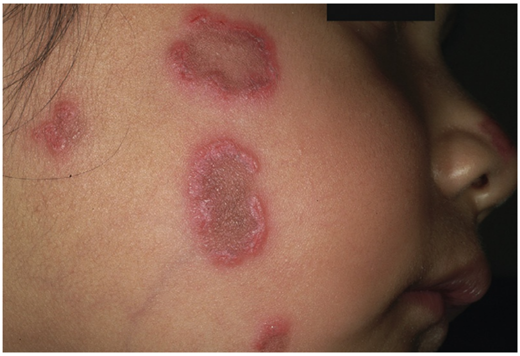

Fig. 17.11 Discoid lupus erythematosus. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*. 5th ed. Philadelphia, PA: Elsevier; 2016:513.)

88. What are the most common manifestations of neonatal lupus erythematosus (NLE)?

The syndrome of *NLE* was first described in babies born to mothers with SLE or Sjögren syndrome; however, it has now been found that 70% to 80% of mothers with these conditions are asymptomatic. NLE is most likely caused by the transmission of maternal IgG autoantibodies. The main manifestations are as follows:

- **Cutaneous:** Skin lesions are found in about 50% of babies with NLE. The rash may be present at birth, but can develop within the first 2 to 3 months of life. Characteristic skin findings are erythematous annular lesions with slightly central atrophy and raised margins, often on the scalp and periorbital region. The periocular rash can give a raccoon-eye appearance (Fig. 17.12). Rash may be precipitated by exposure to sunlight. The lesions are usually transient and nonscarring.

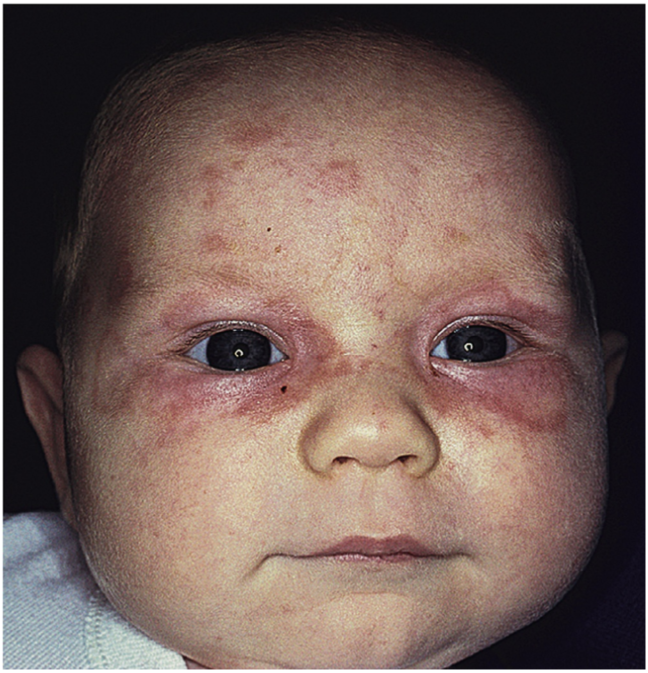

Fig. 17.12 Neonatal lupus erythematosus with “raccoon eyes” and annular forehead plaques. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*. 5th ed. Philadelphia, PA: Elsevier; 2016:519.)

- **Cardiac:** *Complete congenital heart block (CCHB)* is the classic cardiac lesion of NLE; 90% of all CCHB is due to neonatal lupus. Most cases of CCHB appear after the neonatal period, and 40% to 100% of these patients eventually require a pacemaker, usually before they are 18 years old.
- **Hepatic:** Hepatic involvement is seen in at least 15% of babies with NLE. Hepatomegaly with or without splenomegaly is usually seen. Hepatic transaminases are either mild or moderately elevated, or they may be normal. Clinically and histologically, the appearance is often one of idiopathic neonatal giant cell hepatitis.
- **Hematologic:** Thrombocytopenia, hemolytic anemia, and/or neutropenia may be seen.

Vanoni F, Lava SAG, Fossali EF, et al. Neonatal systemic lupus erythematosus syndrome: a comprehensive review. *Clin Rev Allergy Immunol.* 2017;53(3):469–476.

Izmirly PM, Rivera TL, Buyon JP. Neonatal lupus syndromes. *Rheum Dis Clin North Am.* 2007;33(2):267–285.

89. What is the pathophysiology of the CCHB of NLE?

CCHB is caused by **maternal autoantibodies** that cross the placenta and deposit themselves in the conducting system—usually the atrioventricular node—of the fetal heart. This leads to a localized inflammatory lesion, which may then be followed by scarring with fibrosis and calcification. The autoantibodies found are usually anti-Ro antibodies, but anti-La antibodies can also be the etiologic agents.

90. What are the common features of drug-induced lupus?

Fever, **arthralgias** and **arthritis**, and **serositis** can be seen in patients with drug-induced lupus. ANA and antihistone antibodies are often positive, but antibodies to double-stranded DNA are usually negative, and complement levels remain normal. Renal involvement, CNS disease, malar rash, alopecia, and oral ulcers are not usually seen in patients with drug-induced lupus, and their presence should raise suspicion for SLE.

91. What are the most common causes of drug-induced lupus in children?

Antiepileptic medications (especially ethosuximide, phenytoin, and primidone) are the most common causes, and at least 20% of children taking antiepileptic drugs will develop a positive ANA. Minocycline, hydralazine, isoniazid, α-methyldopa, and chlorpromazine are also associated with drug-induced lupus, as are a variety of antithyroid medications and beta blockers. Actually, all of the tetracyclines have been associated with a peculiar lupus-like syndrome that includes the following:

- Acute symmetric polyarthritis
- Positive ANA
- Mild liver dysfunction

Perhaps the most common agent associated with lupus currently is chronic use of minocycline (and other tetracyclines) in association with the treatment of acne. Drug-induced lupus usually resolves within 2 weeks of discontinuation of the medication, but it may last longer (months). It is characterized by arthritis, lupus rash, and hepatitis (persistent “transaminitis”). Other autoantibodies in addition to ANA can be seen as well.

El-Hallak M, Giani T, Yeniay BS, et al. Chronic minocycline-induced autoimmunity in children. *J Pediatr.* 2008;153(3):314–319.

VASCULITIS

92. What clinical features suggest a vasculitic syndrome?

A multisystem disease with **fever**, **weight loss**, and **rash** is often the presenting picture of a vasculitic disorder, which is characterized by the presence of inflammation in a blood vessel wall. Many different types of rashes may be seen, the more common of which are palpable purpura, urticarial vasculitis, and dermal necrosis. CNS involvement, arthritis, myositis, and/or serositis may be seen.

Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, Garcia-Fuentes M. Cutaneous vasculitis in children and adults: associated diseases and etiologic factors in 303 patients. *Medicine.* 1998;77(6):403–418.

93. How are the primary systemic vasculitides classified?

One scheme proposed by an international consensus (European League against Rheumatism/Paediatric Rheumatology European Society [EULAR/PRES]) has classified vasculitides on the basis of the size of the vessels that are predominantly affected, as well as “other vasculitides,” which do not fit well into a vessel size category. In the following list, conditions *in italics* are common pediatric diseases. Conditions marked with an asterisk (*) are not uncommon in pediatric rheumatology centers.

Predominantly large vessel vasculitis

- Takayasu arteritis*

Predominantly medium-sized vessel vasculitis

- *Kawasaki disease*
- Polyarteritis nodosa and its limb-limited variant*

Predominantly small vessel vasculitis

- Microscopic polyangiitis*
- Granulomatosis with polyangiitis (formerly Wegener granulomatosis)*
- Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)*
- Leukocytoclastic vasculitides
- Immune complex mediated: *HSP, lupus vasculitis, serum-sickness vasculitis, drug-induced immune-complex vasculitis, infection-induced immune-complex vasculitis,* Sjögren syndrome vasculitis,* hypocomplementemic urticarial vasculitis*

Other vasculitides

- Behçet disease*
- Paraneoplastic small vessel vasculitis (mostly with acute myelocytic leukemia, ALL, or asparaginase treatment)*
- Inflammatory bowel disease vasculitis, particularly ulcerative colitis–associated stroke and polyarteritis nodosa–like syndrome associated with Crohn disease*

Ozen S, Ruberto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis.* 2006;65(7):936–941.

94. What are the two most common pediatric vasculitides?

HSP (also called *immunoglobulin A vasculitis or IgAV*) and **Kawasaki disease** are the two most common pediatric vasculitides.

95. Which infectious agents are associated with vasculitis?

- **Viral:** human immunodeficiency virus, hepatitis B and C viruses, cytomegalovirus, EBV, varicella virus, rubella virus, and parvovirus B19
- **Rickettsial:** Rocky Mountain spotted fever, typhus, rickettsialpox
- **Bacterial:** meningococcus, disseminated sepsis as a result of any organism, subacute bacterial endocarditis
- **Spirochete:** syphilis
- **Mycobacterial:** tuberculosis

96. What conditions are grouped under the term *pulmonary-renal syndromes*?

These are medical syndromes with alveolar hemorrhage plus glomerulonephritis, which can occur spontaneously or weeks to months apart, and are usually manifestations of autoimmune conditions. Serum autoantibody patterns are helpful in distinguishing the causes (e.g., Goodpasture syndrome is typically positive for anti–glomerular basement membrane antibodies). Symptoms can include dyspnea, fever, and hemoptysis in combination with signs of glomerulonephritis (e.g., edema, hematuria).

- Goodpasture syndrome
- Granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis)
- Eosinophilic granulomatosis with polyangiitis (EGP, formerly Churg-Strauss syndrome)
- SLE

97. What is the clinical triad of Behçet disease?

Aphthous stomatitis, **genital ulcerations**, and **uveitis**. Behçet disease is a vasculitis of unclear etiology. In two-thirds of cases in children, polyarthritis and inflammatory gastrointestinal lesions occur, which can confuse the diagnosis with inflammatory bowel disease, particularly if the patient is <5 years. Aseptic meningitis, sinus vein thrombosis, and other forms of deep vein thrombosis are characteristic of this disease.

98. Should it be "Henoch-Schönlein purpura" or "Schönlein-Henoch purpura"?

In 1837, Johann Schönlein described the association of purpura and arthralgia. Edward Henoch later added the other clinical features, including gastrointestinal in 1874 and renal in 1899. Thus, purists would say that, more properly, the term should be "Schönlein-Henoch purpura." However, in 1801, William Heberden described a 5-year-old boy with joint and abdominal pains, petechiae, hematochezia, and gross hematuria in his *Commentaries on the History and Cure of Disease*, so the true purists might say that, most properly, the condition should be "Heberden syndrome."

99. What are the characteristic laboratory findings of patients with HSP?

Acute-phase reactants, including the ESR and C-reactive protein, are commonly elevated, and there is frequently a mild leukocytosis. Thrombocytopenia is never seen. Microscopic hematuria and proteinuria are indicators of renal involvement. HSP appears to be an immunoglobulin A (IgA)–mediated illness; elevated serum IgA has been noted and has been demonstrated by immunofluorescence in skin and renal biopsies. (The renal histology is indistinguishable from Berger disease.) Circulating immune complexes and cryoglobulins containing IgA are also commonly seen.

Trnka P. Henoch-Schönlein purpura in children. *J Paediatr Child Health.* 2013;49(12):995–1003.

100. What kinds of skin lesions are noted in patients with HSP?

HSP is one of the *hypersensitivity vasculitides* and, as such, is characterized by leukocytoclastic inflammation of arterioles, capillaries, and venules. Initially, **urticarial** lesions predominate, and they may itch or burn; these develop into pink **maculopapules**. With damage to the vessel walls, there is bleeding into the skin, which results in nonthrombocytopenic **petechiae** and **palpable purpura** (papules and plaques), typically located on the buttocks and lower extremities (Fig. 17.13). A migrating soft tissue edema is also commonly seen in younger children.

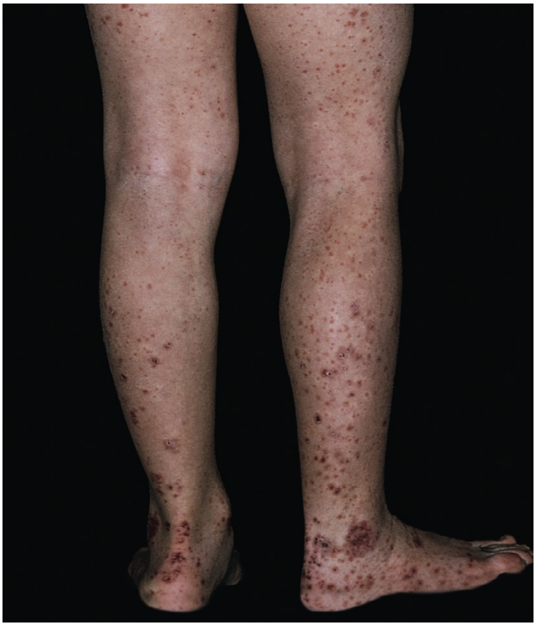

Fig. 17.13 Henoch-Schönlein purpura with numerous palpable purpuric papules and plaques on the legs and feet. (From Habif TP. *Clinical Dermatology.* 6th ed. Philadelphia, PA: Elsevier; 2016:736.)

101. In addition to the skin, what other organ systems are typically involved in HSP?

Classically, HSP involves the musculoskeletal system, the gastrointestinal tract, and/or the kidneys.

- The most common abdominal finding is **gastrointestinal** colic (70%). This is frequently associated with nausea, vomiting, and gastrointestinal bleeding. These findings may precede the skin rash in $\leq$30% of cases. Intussusception occurs in $\leq$5% of cases.
- **Renal** involvement occurs in about 50% of reported cases, and it is usually apparent early during the course of the illness. It ranges in severity from microscopic hematuria to nephrotic syndrome.
- **Joint** involvement is very common (80%) and can be quite painful. Periarticular swelling of the knees, ankles, wrists, and elbows—rather than a true arthritis—is usually seen.
- Up to 15% of males can have **scrotal** involvement with epididymitis, orchitis, testicular torsion, and scrotal bleeding.
- **Pulmonary** hemorrhage is a rare complication of HSP that is mainly seen among adolescents and adults. It is associated with significant mortality.

Trnka P. Henoch-Schönlein purpura in children. *J Paediatr Child Health.* 2013;49(12):995–1003.

102. How often does chronic renal disease develop in children with HSP?

The long-term prognosis of patients with HSP depends mainly on the initial renal involvement. Overall, $<$5% of patients with HSP develop end-stage renal disease. However, up to two-thirds of children who have severe crescentic glomerulonephritis documented on biopsy will develop terminal renal failure within 1 year. Of those with nephritis or nephrotic syndrome at the onset of illness, almost half may have long-term problems with hypertension or impaired renal function as adults. Microscopic hematuria as the sole manifestation of HSP is common and is associated with a good long-term outcome.

Chan H, Tang YL, Lv XH, et al. Risk factors associated with renal involvement in childhood Henoch-Schönlein purpura: a meta-analysis. *PLoS One.* 2016;11(11):e0167346.

Coppo R, Andrulli S, Amore A, et al. Predictors of outcome in Henoch-Schönlein purpura in children and adults. *Am J Kidney Dis.* 2006;47(6):993–1003.

KEY POINTS: HENOCH-SCHÖNLEIN PURPURA

1. A small vessel vasculitis (also called *IgA vasculitis*)
2. The classic clinical triad is as follows: purpura, arthritis, and abdominal pain.
3. One-half of patients have abnormal urinalyses (hematuria, proteinuria; usually mild).
4. Steroid therapy is debated, but it should be considered for painful arthritis, abdominal pain, nephritis, edema, and scrotal swelling.
5. A few patients have long-term renal complications.

103. Why is the diagnosis of intussusception often difficult in patients with HSP?

- Intussusception can occur suddenly, without preceding abdominal symptoms.
- Nearly one-half of cases of HSP intussusception are ileoileal (compared with non-HSP intussusceptions, of which 75% are ileocolic). This increases the likelihood of a false-negative barium enema.
- The variety of possible gastrointestinal complications in patients with HSP (e.g., pancreatitis, cholecystitis, gastritis) can confuse the clinical picture.
- The common occurrence (50% to 75%) of melena, guaiac-positive stools, and abdominal pain in HSP without intussusception may lead to a lowered index of suspicion.

104. When are corticosteroids indicated for the treatment of HSP?

The precise indications for corticosteroids in patients with HSP remain controversial. Corticosteroids do produce rapid improvements in symptoms, but it is uncertain if treatment changes the long-term clinical outlook, particularly in the prevention of renal complications. Toxicity is always a concern, so the duration of therapy and the dosing should be judicious, with tapering planned at inception. Prednisone, 1 to 2 mg/kg per day (maximum: 80 mg/kg per day), is administered for 7 days, which can be followed by tapering over 2 to 3 weeks depending on symptoms at onset. In patients with severe intestinal symptoms, steroids may decrease the likelihood of intussusception, and studies have shown that they reduce surgical interventions. Corticosteroids are helpful in the settings of significant pulmonary, scrotal, or CNS manifestations to minimize vasculitic inflammation; they are sometimes used if severe joint pain is present and NSAIDs are ineffective or there is gastrointestinal bleeding. Steroids do not prevent the recurrence of symptoms, and symptoms may flare when steroids are discontinued.

Jauhola O, Ronkainen J, Koskimies O, et al. Outcome of Henoch-Schönlein purpura 8 years after treatment with a placebo or prednisone at disease onset. *Pediatr Nephrol.* 2012;27(6):933–939.

Weiss PF, Feinstein JA, Luan X, et al. Effects of corticosteroid on Henoch-Schönlein purpura: a systematic review. *Pediatrics.* 2007;120(5):1079–1087.

105. What is acute hemorrhagic edema of infancy (AHEI)?

A simplistic answer is that *AHEI* is an infantile version of HSP, appearing during the first and second years of life. Erythematous, palpable, large purpuric lesions develop over a 1- to 2-day period and, when confluent, are quite dramatic in appearance. (The French call it the "rosette," and the English call it the "knot of ribbons.") Skin lesions are seen in the upper and lower extremities and on the face, particularly in the ears. IgA deposition is common around the vasculitic lesions. Renal and gastrointestinal involvements are rare, and complete recovery is the rule in 2 to 3 weeks. The pathogenesis is felt to involve immune complex deposition in response to an antigenic trigger. An infectious prodrome is noted in two-thirds of cases. AHEI is also known as *Finkelstein syndrome*.

Rohr BR, Manalo IF, Mowad C. Acute hemorrhagic edema of infancy: guide to prevent misdiagnosis. *Cutis.* 2018;102(5):359–362.

106. In which rheumatic diseases can "cauliflower ears" be seen?

"Cauliflower ears," which involve swelling under the perichondrium of the pinna (as classically observed in wrestlers or boxers), can be seen in babies with *AHEI* and in older children with *relapsing polychondritis*—a potentially serious disease primarily affecting cartilage of the ears, airways, sclera, and aortic valve ring.

107. What is the difference between autoimmune and autoinflammatory diseases?

Both conditions result in the immune system attacking the body's own tissues.

- *Autoimmune diseases* result from problems with *adaptive (or acquired) immunity,* which refers to the more complex antigen-specific immune response (e.g., lymphocytes) and the production of autoantibodies.
- *Autoinflammatory diseases* are a group of conditions that involve deregulation of the inflammatory cascade in the absence of autoantibodies (such as ANA, RF, and antineutrophil cytoplasmic antibodies [ANCA]).

The autoinflammatory problem is believed to involve dysregulation of *innate immunity*. This is the branch of the immune system characterized by nonspecific immune defenses (e.g., neutrophils and monocytes). *Autoinflammatory diseases* are incompletely understood, but many are characterized by genetic mutations, which result in increased and frequent activation of inflammatory pathways. Inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, are overproduced. Unlike autoimmune diseases, autoantibodies are not driving the inflammation. Autoinflammatory diseases are characterized by chronic and recurrent episodes of systemic and organ-specific inflammation, with fever, particularly recurrent, as a prime symptom.

Hausmann JS, Dedeoglu F. Autoinflammatory diseases in children. *Dermatol Clin.* 2013;31(3):481–494.

108. How sharp is the separation between these two disease categories?

As with most scientific advances, the more we know, the more exceptions we find in our definitions and ambiguity in our classifications. A growing group of Mendelian autoinflammatory disorders are exhibiting autoimmune features. This emerging category has been called *type I interferonopathies* because of the relevant role of a defective regulation of interferon activation in their pathogenesis. As with many disease entities, the acronyms can be catchy, including CANDLE (**c**hronic **a**typical **n**eutrophilic **d**ermatosis with **l**ipodystrophy and **e**levated temperature) and SAVI (**s**ting-**a**ssociated **v**asculopathy of **i**nfancy).

Volpi S, Picco P, Caorsi R, et al. Type I interferonopathies in pediatric rheumatology. *Pediatr Rheumatol Online J.* 2016;14(1):35.

109. Are all autoinflammatory diseases characterized by periodic fever and genetic mutations?

No, and this can make the diagnostic process difficult. More than 30 monogenetic autoinflammatory diseases have been identified. A group associated with mutations in the *NLRP3* gene (NOMID and Muckle-Wells) are chronic rather than periodic. Among the periodic fevers are familial Mediterranean fever, TNF-associated periodic fever syndrome (TRAPS), and hyperimmunoglobulin D syndrome (HIDS). PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome, also known as *Marshall syndrome,* has no known genetic basis, although it has many of the features of an autoinflammatory disorder.

Sag E, Bilginer Y, Ozen S. Autoinflammatory diseases with periodic fevers. *Curr Rheumatol Rep.* 2017;19(7):41.
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